EFFECT OF SUPERDISINTEGRANTS CONCENTRATION ON DISSOLUTION PROFILE OF POORLY SOLUBLE ANTIVIRAL DRUG

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LUTE ATULKUMAR RAMDASRAO

Reg.No. 26106306

Under the guidance of

INSTITUTIONAL GUIDE

Mr. Barish, M.Pharm,**FICS.,FAGE.,**
Assistant Professor
Department of Pharmaceutics
R.V.S .College of Pharmaceutical
Sciences, Sulur, Coimbatore, Tamil Nadu.

INDUSTRIAL GUIDE

Dr. Vinay U. R.,M.Pharm, Ph.D.,
AVP, PDL & TT Dept., Aurobindo
Pharma. Ltd., Unit-VII, Jadcherla,
SEZ (APIIC), Andhra Pradesh.

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SULUR, COIMBATORE

1. INTRODUCTION [37,39,43,44,68]

In any type of tablet system, the important variable is the rate at which the active substance goes into solution or dissolves. Superdisintegrants such as Crospovidones, Sodium Starch Glycolate, and Croscarmellose Sodium are now frequently used in tablet formulations to improve the rate and extent of tablet disintegration and thus increase the rate of drug dissolution. The bioavailability of drug is dependent on in-vivo disintegration, dissolution, and various physiological factors. In recent years, scientists have focused their attention on the formulation of quickly disintegrating tablets.

Therapeutic effectiveness of a drug depends upon the bioavailability and the solubility of the drug molecules. Solubility is one of the important parameter to achieve the desired concentration of the drug in systemic circulation for pharmacological response to be shown. Currently only 8% of the drugs were having high solubility and high permeability. Dissolution of drug from a dosage form involves at least two consecutive steps. Liberation of the solute or drug from the formulation matrix (disintegration), followed by dissolution of the drug (solubilisation of the drug particles) in the liquid medium. The overall rate of dissolution depends on the slower of these two steps. The relative difference in rates should be carefully considered when designing the dissolution method.

Despite a rising interest in release drug delivery systems, the most common tablets that are intended to be swallowed whole, which disintegrates to release their medicaments rapidly in the gastro intestinal tract, still remain the dosage form of choice for most of the drugs**.** A number of studies have been published describing the effect of operating conditions on granule quality and the optimization of the process. For example, the effects of nine different high speed mixers on the porosity and size distribution of granules. There is use of a computer optimization technique based on response surface methodology to scale up wet granulation process. The discussion of factors critical to obtaining granules with desirable physical properties in granulation by high speed mixer is important. Evaluation of the granulation end point from the perspective of power consumption change is also useful. Disintegrants vary widely and have different mechanisms of action ranging from passive solubilisation to the

wicking effect of cross linked polysaccharides and the "explosive" type action of the superdisintegrants.

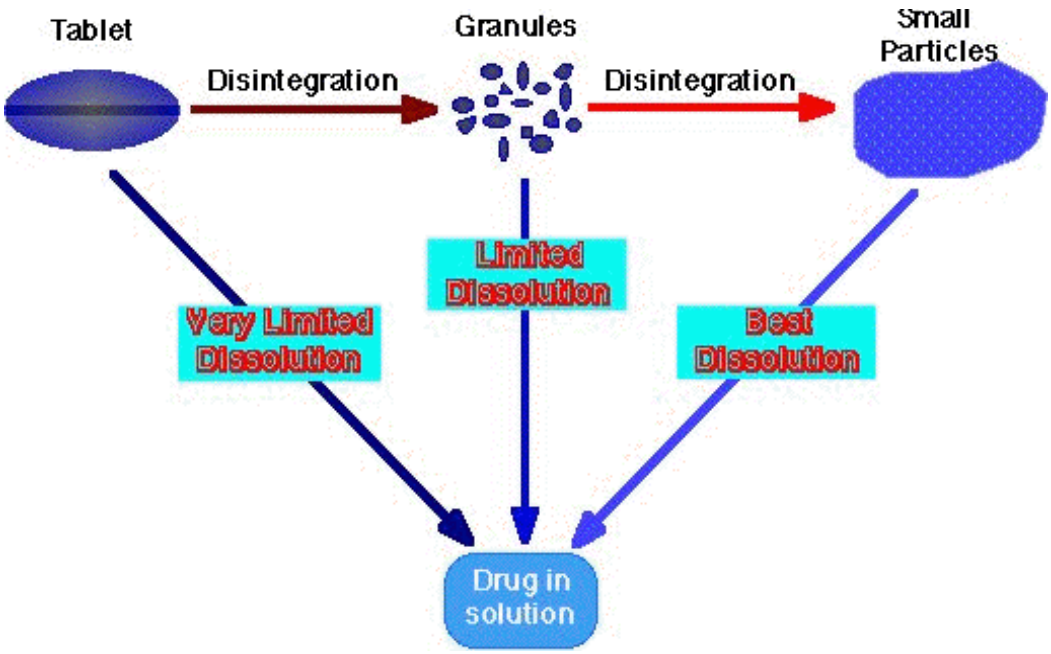


Fig No.1.1: Dissolution Mechanism

Mechanism [56,57]

The active constituents must be released from the tablet as efficiently as possible to allow its rapid action. The mechanism of action had shown in Fig No: 2, 3 and its action in Table No: 1.The mechanism by which the tablets are broken into small pieces and then produces a homogeneous suspension is based on:

- Capillary action
- High swellability
- Heat of wetting
- Particle – particle repulsive forces
- Deformation
- Release of Gases
- By enzymatic action.

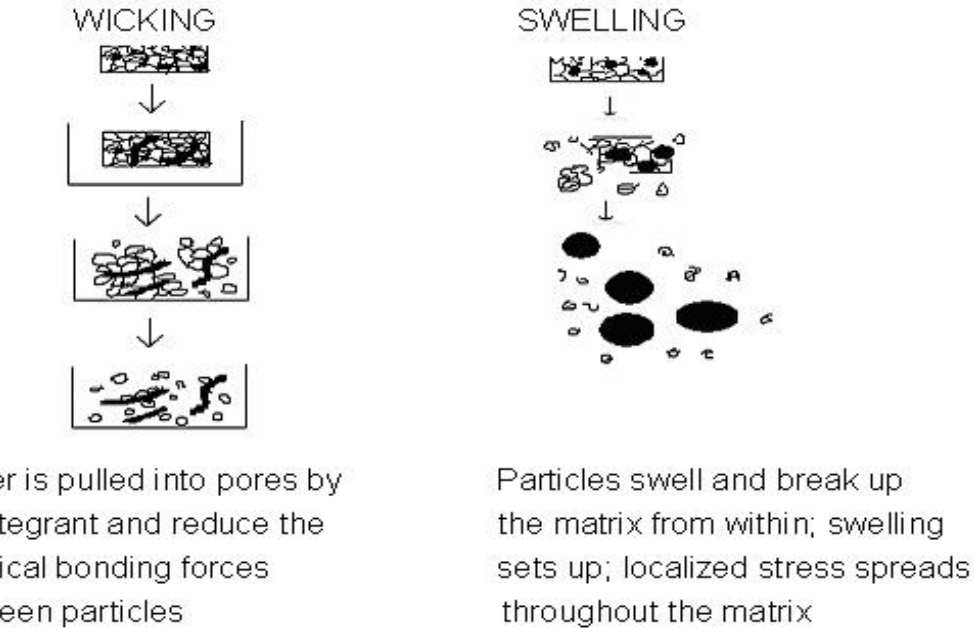
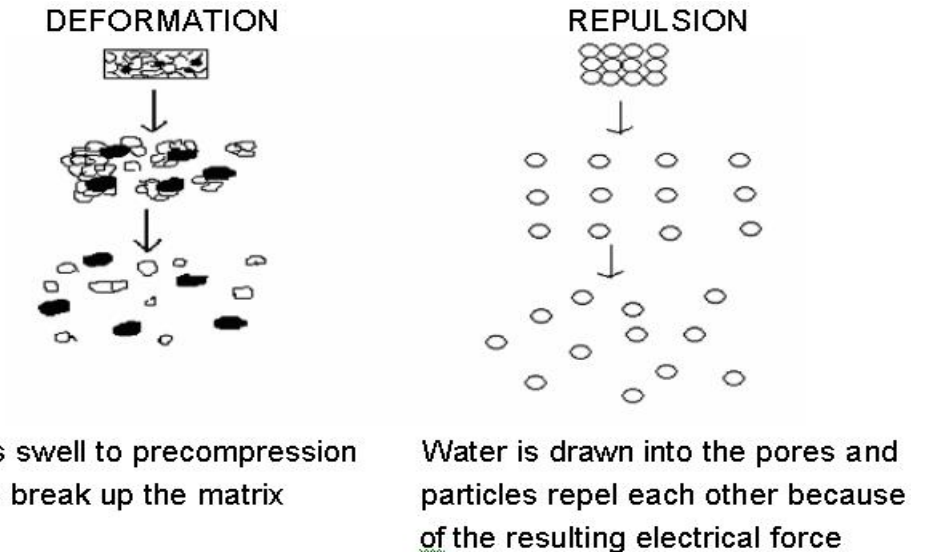


Fig No.1.2 : Disintegration of tablet by wicking and swelling



No.1.3 : Disintegration by deformation and repulsion

Table No.1.1: Mechanism of action of some Superdisintegrants

S.NO.	Superdisintegrants	Mechanism of action
1.	Ac-di-sol	Swelling
2.	Polyplasdone XL Polyplasdone XL-10	Swells very little, return to original size after compression but act by capillary action
3.	SSG	Swelling
4.	MCC	Wicking

Method of Addition of Disintegrants [45]

Disintegrants are essentially added to tablet granulation for causing the compressed tablet to break or disintegrate when placed in aqueous environment. There are three methods of incorporating disintegrating agents into the tablet:

- Internal Addition (Intragranular)
- External Addition (Extragranular)
- Partly Internal and External

Factors affecting action of Disintegrants [45]

- Percentage of disintegrants present in the tablets.
- Types of substances present in the tablets.
- Combination of disintegrants.
- Presence of surfactants.
- Hardness of the tablets.
- Nature of Drug substances.
- Mixing and Screening

Besides these factors, one which influences the disintegrant action is its mode of incorporation of disintegrants. In general, croscarmellose sodium and sodium starch glycolate were found to be less sensitive to the mode of incorporation than crospovidone**.**

The present invention relates to compressed tablets of some poorly soluble antiviral drugs that contain one or more disintegrants that enhance the dissolution rate of the efavirenz in the gastrointestinal tract thereby improving the rate and extent of absorption of the drug to the body. In addition to the active ingredient, solid dosage forms contain a number of additional ingredients referred to as excipients. These

excipients include among others diluents, binders, lubricants, glidants and disintegrants. Diluents are used to impart bulk to the formulation to make a tablet a practical size for compression. Examples of diluents are lactose and cellulose. Binders are agents used to impart cohesive qualities to the powdered material ensuring the tablet will remain intact after compression, as well as improving the free-flowing qualities of the powder. Examples of typical binders are lactose, starch and various sugars. Lubricants have several functions including preventing the adhesion of the tablets to the compression equipment and improving the flow of the granulation prior to compression or encapsulation. Lubricants are in most cases hydrophobic materials. Excessive use of lubricants can result in a formulation with reduced disintegration and/or delayed dissolution of the drug substance. Glidants are substances that improve the flow characteristics of the granulation material. Examples of glidants include talc and colloidal silicon dioxide**.**

Many drugs, both in development and already available in the market, have the problem of being only poorly soluble in aqueous media (e.g. Efavirenz). The fact that more than 40% of newly discovered drugs have little or no water solubility presents a serious challenge to the successful development and commercialization of new drugs in the pharmaceutical industry. The present study compared various superdisintegrants in terms of physicochemical properties by using antiviral drugs by wet granulation method, by improving the dissolution characteristics. Because, all the superdisintegrants having different mechanisms by acting (e.g. swelling, wicking etc.).

2. OBJECTIVE

The objective of the present investigation was to study, to understand the effect of superdisintegrants like crospovidones (Polyplasdone XL, XL-10), Croscarmellose Sodium and Sodium Starch Glycolate on the dissolution profiling of some poorly soluble anti-viral drugs from their respective tablets. For this study four different Superdisintegrants were selected. The two grades of crossprovidone differ by particle size.

- Croscarmellose Sodium (Ac-di-sol)
- Sodium Starch Glycolate (SSG)
- Polyplasdone XL Crossprovidone (PVPPXL)
- Polyplasdone XL-10 Crossprovidone (PVPPXL10)

For the present study

Comparison of Polyplasdone XL and XL-10 crossprovidone with innovator product (e.g. SUSTIVA) by using wet granulation method.

Model drugs were having various solubility according to British Pharmacopoeia were selected. For these study three poorly soluble anti-viral drugs were selected and having high market strength.

- Efavirenz 600mg (SUSTIVA)- Practically insoluble in water
- Acyclovir 800mg (ZOVIREX)- Slightly soluble in water
- Nevirapine 200mg (VIRAMUNE)- Sparingly soluble in water

Rationale for work

Disintegrants under its consistency of performance are of critical importance to the formulation of tablets. In these studies, three antiviral drugs having higher marketed dose were selected. The effect of superdisintegrants at 5% use level in the tablet formulation on the *in vitro* dissolution in sink (Compendia or U.S. Food and Drug Administration recommended) medium and quasi-sink dissolution medium were evaluated.

3. PLAN OF STUDY AND STUDY PROTOCOL

3.1. PLAN OF STUDY

The present work is to study the effect of four superdisintegrants on three anti-viral drugs Efavirenz, Acyclovir and Nevirapine by wet granulation techniques. In the present study tablets were prepared at approximately equal hardness. The dissolution profiles of drugs were compared for tablets containing different Superdisintegrants, then to compare the effect of superdisintegrants effect on the invitro dissolution in compendia medium and quasi-sink dissolution medium. Then stability studies for three months at three different conditions according to ICH guidelines.

3.2. STUDY PRTOCOL

Tablets were prepared by wet granulation method.

Tablets are to be characterized for the following parameters

- Loss on Drying
- Bulk and Tapped Density
- Hardness
- Friability
- Disintegration time
- Assay for granules and tablets

In-vitro dissolution study by using USP apparatus 2 (Paddle).Determination of DE30 and T_{50} and T_{80}.Stability studies for three months at three different conditions according to ICH guideline.

4. LITERATURE REVIEW

4.1. REVIEW ON DRUG AND EXCIPIENTS

Marier J F et al [32] They reported that the efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that has been used successfully for more than a decade to treat Human Immuno Deficiency Virus (HIV) infection**.**

Gao J Z et al [15] They reported that the efavirenz is a poorly water soluble and highly permeable drug and investigated pharmacoscintigraphic behavior of two tablets (efavirenz) and suggested that the difference in in-vivo performance between the two tablet and capsule formulations is due to a different rate of in-vivo disintegration and suggest that for this drug the in-vivo dissolution and disintegration were more important factor affecting the rate and extent of drug absorption**.**

Starr S E et al [47] They investigated that the safety, pharmacokinetics, anti viral activity and immunologic effects of efavirenz liquid formulation, with nelfinavir a nucleoside reverse transcriptase inhibitor (NRTI) in HIV infected children, 3 to 9 years of age, concluded that combination therapy of liquid formulation with nelfinavir is an attractive treatment option for HIV infected children below 3 years of age who are unable to take efavirenz capsules**.**

Choudhary K P R et al [12,45] They suggested that the poor dissolution characteristics of relatively insoluble drugs have long been a problem to the pharmaceutical industry. When an insoluble or sparingly soluble drug is administered orally, the rate and extent of absorption are controlled by the dissolution rate in the gastro intestinal fluids. They suggested the techniques like solid dispersion and use of hydrophilic matrix, prodrug approach, complex formation and use of buffering agents, surfactants, superdisintegrants to enhance the dissolution and bio-availability of poorly soluble drugs.

Cacace J et al [9] They studied that the comparison of the dissolution of Metaxalone Tablets (Skelaxin) Using USP Apparatus 2 and 3. The purpose of this study was to evaluate the effect of pH on the dissolution behavior of metaxalone in the marketed product Skelaxin tablets. The dissolution was evaluated using United

States Pharmacopoeia (USP) dissolution Apparatus 2 and 3 at pHs ranging from 1.5 to 7.4. Results from these studies show that the dissolution of this product is pH dependent. At low pH (simulated gastric fluid, pH 1.5), the dissolution of metaxalone from Skelaxin tablets was less than 10% over 75 minutes; whereas, dissolution at pH 4.5 showed greater than 90% release in the same time period. These results were consistent for both Apparatus 2 and 3. This suggests that Skelaxin Tablets should be considered a delayed release dosage form.

Watanable Y et al [52] They reported that the cellulose such as purified cellulose, methylcellulose, crosslinked sodium carboxy methylcellulose (Ac-Di-Sol) and carboxy methyl cellulose are disintegrants to some extent depending on their ability to swell on contact with water. A crosslinked form of Ac-Di-Sol has been accepted as tablet disintegrant and it is essentially water insoluble. It has high affinity for water, which results in rapid tablet disintegration.

Augsburger et al [5] They had shown the mechanism of action of disintegrants such as Ac-Di-Sol primogel, polyplasdone XL-10 and corn starch by rapid liquid absorption and swelling of disintegrant particles which fills the void spaces and cause the compact to disintegrate rapidly. Disintegrants, however, varied widely in their wicking and swelling properties and minimum concentration of disintegrant is necessary to produce primary particles upon disintegration and effectively improve drug dissolution. This study was thus designed to examine the behavior of disintegrant in their pure state and in hard gelatin capsule formulations. The intrinsic ability of disintegrant to absorb water and swelling was measured.

Modi A et al [35] They investigated enhancement of the dissolution profile of valdecoxib using solid dispersion with PVP and also described the preparation of fast dissolving tablets of valdecoxib by using a high amount of superdisintegrants. They reported the dissolution of valdecoxib improved significantly in solid dispersion products.

Thibert R et al [49] They studied the effects of milling with a ball mill on the physical properties and functional behavior of the superdisintegrants SSG (Explotab), ac-di-sol, crospovidone. The result showed the milling decrease particle size and

increased the surface area of superdisintegrants and no effect on moisture uptake behavior.

Alsaidan S M et al [3] They studied improved dissolution rate of indomethacin by adsorbents. Samples of indomethacin and kaolin or microcrystalline cellulose (Avicel) were prepared by solvent deposition or simple blending methods. Dissolution rates of these samples were studied. The surface adsorption of indomethacin on the studied adsorbents was shown to improve the dissolution rate of the drug in water. The solvent-deposited samples of indomethacin on kaolin or Avicel in the ratio 1:4 released 25% of the drug at 34 or 60 min, respectively (t_{25}%), while 25% of the pure drug was released at 140 min. Meanwhile, the t_{25}% of the corresponding drug-adsorbent simple blends was 108 and 110 min, respectively. The effect of addition of polyvinyl pyrrolidone (PVP) as a third component to indomethacin-adsorbent was studied and showed further improvement in in-vitro availability of the drug-kaolin adsorbent**s.**

Zhao N , Augsburger LL et al [57] They studied that the disintegration efficiency, and to develop a discriminating test model for the 3 classes of superdisintegrants represented by Ac-Di-Sol, Primojel, and Polyplasdone XL-10. Using a digital video camera to examine the disintegration process of tablets containing the same wt/wt percentage concentration of the disintegrants, Ac-Di-Sol was found to disintegrate tablets rapidly into apparently primary particles; Primojel also apparently disintegrated tablets into primary particles but more slowly; Polyplasdone XL-10 disintegrated tablets rapidly but into larger masses of aggregated particles. The differences in the size distribution generated in the disintegrated tablets likely contribute to the drug dissolution rate differences found for aspirin tablets with similar disintegration rates. The aspirin tablet matrix is proposed as a model formulation for disintegrant efficiency comparison and performance consistency testing for quality control purposes.

Zhao N et al [58] They studied the causes of efficiency loss of superdisintegrants following granulation or reworking. Two processes, precompression and prewetting, were proposed to simulate the processes during dry and wet granulation, respectively. The disintegration efficiency of the resulting disintegrant granules was tested in model formulations composed of dicalcium

phosphate and lactose with the unprocessed disintegrants as controls. No significant difference was shown in the intrinsic swelling and the water uptake abilities of all super disintegrants following dry granulation. However, a significant decrease was observed for both Primojel and Polyplasdone XL-10 in the rate of water being absorbed into the tablet matrix following wet granulation, but not for Ac-Di-Sol. United States Pharmacopoeia (USP) disintegration testing without disc revealed a significant increase in disintegration time for tablets formulated with dry granulated Primojel and Polyplasdone XL-10 and all wet granulated disintegrants. The increase in particle size following granulation appears to be the cause of the loss in disintegration efficiency. In conclusion, Ac-Di-Sol is less affected by both precompression and prewetting. The efficiency of Primojel and Polyplasdone XL-10 is highly dependent on their particle size. Decreasing the particle size tends to increase their efficiency. Due to the size increase following granulation, a higher addition level of superdisintegrant is required to ensure fast and uniform disintegration of tablets prepared by granulation.

Souto C et al [46] They studied the utility of including superdisintegrants (croscarmellose sodium or sodium starch glycolate) in microcrystalline cellulose extrusion-spheronization pellets as a means of increasing the dissolution rate of poorly water-soluble drugs. The model drug was hydrochlorothiazide, with water or water/ethanol as wetting agent for pellet preparation. Neither disintegrant had significant effects on pellet morphology, flow properties or mechanical resistance. Nevertheless, the disintegrants afforded a modest increase in drug dissolution rate, attributable to the observed increase in pellet micropore volume. Drug dissolution rate was slightly higher in pellets prepared with sodium starch glycolate; probably because of this disintegrants higher swelling capacity.

Maria de la Luz Reus Medina et al [31] They studied the evaluation of cellulose II powders as a potential multifunctional excipient in tablet formulations. They concluded that UICEL-A/102 and UICEL-XL have the potential to be used as filler, binder, and disintegrant, all-in-one, in the design of tablets containing either a low dose or high dose drug by the direct compression method.

Patel D M et al [38] They prepared the tablet formulation of piroxicam containing PVRK 30 and SLS. It showed the formulation increases the dissolution profiles.

Watari Nobutoshi et al [51] They studied the dissolution of Slightly Soluble Drugs. II. Effect of Particle Size on Dissolution Behavior in Sodium Lauryl Sulfate Solutions. Experiments were made to compare the effect of particle size of sulfonamide on the initial dissolution behavior in sodium lauryl sulfate solution and in distilled water and the following results were obtained. 1) At agitation speed of 700 rpm, there was no difference of particle size on the initial dissolution in 0.1% and in distilled water but in 1% solution somewhat, and the difference appeared at agitation speed of 300 rpm with decrease in particle size. Results obtained in sodium lauryl sulfate solution showed a similar tendency while the instantly dissolving part increased with decrease in particle size, and this part dissolved instantly at first and the constant rate of dissolution followed in distilled water. 2) Plots of log dissolution rate constants vs. log agitation speed became linear with the same slope irrespective of particle size, when 0.1% and 1% solutions were used. Rank order for the dissolution rates of different particle size of powders was possible even at a relatively low agitation speed of 200 rpm.

Mukesh C Gohel et al [36] They studied that the improvement of nimesulide dissolution from solid dispersions containing croscarmellose sodium and Aerosil 200 was found to be >200. They concluded that the Aerosil effective in increasing the drug dissolution compared to croscarmellose sodium.

Yen S Y et al [55] They studied the dissolution enhancement of nifedepine but the solvent deposition techniques on superdisintegrants including ac-di-sol, Kollidon CL, SSG, it showed significantly enhanced the rate of dissolution of nifedipine.

Jayesh Parmar & Manish Rane [69] They gave information about the oral dosage form because, the process of manufacturing tablets is complex. Hence, careful consideration payed to select right process,and right excipients to ultimately give a robust, high productivity and regulatory compliant product of good quality.

4.2. API SPECIFICATIONS

4.2.1. EFAVIRENZ [15,32,47,67]

Efavirenz is a human immunodeficiency virus type 1 (HIV-1) specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI).

Capsules

Efavirenz is available as capsules for oral administration containing either 50 mg, 100 mg, or 200 mg of efavirenz

Tablets

Efavirenz is available as film-coated tablets for oral administration containing 600 mg of efavirenz.

Brand name: EFA, STOCRIN, SUSTIVA.

Chemical Name

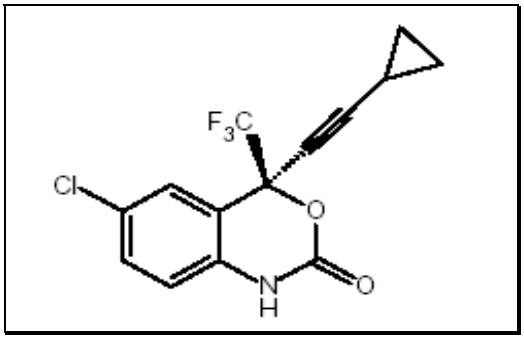
8-chloro-5-(2-cyclopropylethynyl)-5-(trifluoromethyl)-4-oxa-2-azabicyclo[4.4.0] deca-7,9,11-trien-3-one.

Empirical Formula $C_{14}H_9ClF_3NO_2$

Molecular Weight 315.68

Melting Point 139-141 °C

Structural Formula



Solubility

Practically insoluble in water (<10 mg/mL).

Mechanism of Action

Efavirenz falls in the non-nucleoside reverse transcriptase inhibitor (NNRTI) class of antiretroviral. Both nucleoside and non-nucleoside RTIs inhibit the same target, the reverse transcriptase enzyme, an essential viral enzyme which transcribes viral RNA into DNA. Unlike nucleoside RTIs, which bind at the enzyme's active site, NNRTIs bind within a pocket termed the NNRTI pocket.

Pharmacokinetics

The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency; however, less than 1% of efavirenz is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal. A multiple-dose study showed no significant effect on efavirenz pharmacokinetics in patients with mild hepatic impairment (Child-Pugh Class A) compared with controls. There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh Class B or C) affects efavirenz pharmacokinetics

Absorption

Peak efavirenz plasma concentrations of 1.6-9.1 mM were attained by 5 hours following single oral doses of 100 mg to 1600 mg administered to uninfected volunteers. Dose-related increases in C_{max} and AUC were seen for doses up to 1600 mg; the increases were less than proportional suggesting diminished absorption at higher doses.

Distribution

Efavirenz is highly bound (approximately 99.5-99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (n=9) who received efavirenz 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Metabolism

Studies in humans and in vitro studies using human liver microsomes have demonstrated that efavirenz is principally metabolized by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The in-vitro studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism.

Elimination

Efavirenz has a terminal half-life of 52-76 hours after single doses and 40-55 hours after multiple doses. A one-month mass balance/excretion study was conducted using 400 mg per day with a ^{14}C-labeled dose administered on Day 8. Approximately 14-34% of the radiolabel was recovered in the urine and 16-61% was recovered in the feces. Nearly all of the urinary excretion of the radio labeled drug was in the form of metabolites. Efavirenz accounted for the majority of the total radioactivity measured in feces.

Drug Interactions

Efavirenz has been shown in-vivo to cause hepatic enzyme induction, thus increasing the biotransformation of some drugs metabolized by CYP3A4.

Indications

Efavirenz in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on two clinical trials of at least one year duration that demonstrated prolonged suppression of HIV- RNA.

Dosage and administration

The recommended dosage of efavirenz is 600 mg orally, once daily, in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs). It is recommended that efavirenz be taken on an empty stomach, preferably at bedtime. The increased efavirenz concentrations

observed following administration of efavirenz with food may lead to an increase in frequency of adverse events

Side effects

The most significant adverse events observed in patients treated with efavirenz are nervous system symptoms, psychiatric symptoms, and rash.

Contraindications

Efavirenz is contraindicated in patients with clinically significant hypersensitivity to any of its components. Efavirenz should not be administered concurrently with artemizole, voriconazole, cisapride, midazolam, triazolam, or ergot derivatives.

4.2.2. ACYCLOVIR

Acyclovir is a synthetic nucleoside analogue active against herpes viruses.

Capsules

Acyclovir is available as capsules for oral administration containing 200 mg of acyclovir.

Tablets

Acyclovir is available as for oral administration containing 800 mg and 400mg of acyclovir.

Suspension

Each teaspoonful (5 mL) of acyclovir Suspension contains 200 mg of acyclovir.

Brand name ZOVIRAX

Chemical Name

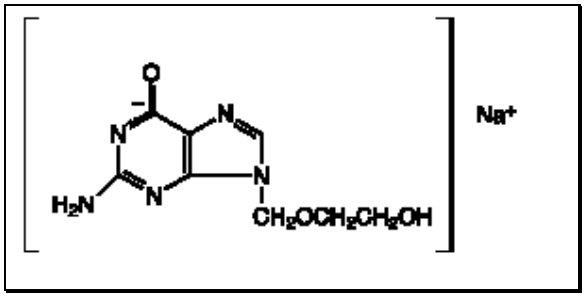
2-amino-1, 9-dihydro-9-[(2-hydroxyethoxy) methyl]-6H-purin-6-one

Empirical Formula $C_8H_{11}N_5O_3$

Molecular Weight 225.205 g/mol

Melting Point 256.5 - 257 °C

Structural Formula



Solubility

The maximum solubility in water at 37° C is 2.5 mg/mL.

Mechanism of Action

Acyclovir is a synthetic purine nucleoside analogue with in-vitro and in-vivo inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV).

Pharmacokinetics

The pharmacokinetics of acyclovir after oral administration have been evaluated in healthy volunteers and in immunocompromised patients with herpes simplex or varicella-zoster virus infection. Acyclovir pharmacokinetic parameters are summarized in Table No.4.1.

Table No: 4.1 Acyclovir Pharmacokinetic Characteristics (Range)

Parameter	Range
Plasma protein binding	9% to 33%
Plasma elimination half-life	2.5 to 3.3 hr
Average oral bioavailability	10% to 20%*

*Bioavailability decreases with increasing dose.

Drug Interactions

Coadministration of probenecid with intravenous acyclovir has been shown to increase the mean acyclovir half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

Indications

Herpes Zoster Infections, Genital Herpes, Chickenpox**.**

Side effects

Anaphylaxis, angioedema, fever, headache, pain, peripheral edema.

Contraindications

Acyclovir is contraindicated for patients who develop hypersensitivity to acyclovir or valacyclovir.

4.2.3. NEVIRAPINE

Nevirapine is a non-nucleoside reverse transcriptase inhibitor with activity against Human Immunodeficiency Virus Type 1 (HIV-1).

Tablets

Nevirapine is tablets for oral administration containing 200 mg of nevirapine.

Suspensions

Each 5 mL of Nevirapine suspension contains 50 mg of nevirapine (as nevirapine hemihydrates).

Brand name VIRAMUNE

Chemical Name

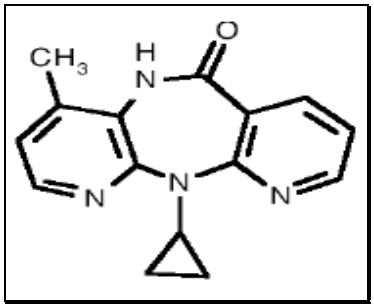
11-cyclopropyl-5, 11-dihydro-4-methyl-6H-dipyrido [3,2-b:2', 3'-e][1,4] diazepin-6-one

Empirical Formula $C_{15}H_{14}N_4O$

Molecular Weight 266.298 g/mol

Melting Point 196.06

Structural Formula



Solubility:

Sparingly soluble in water (0.7046 mg/L)

Mechanism of Action

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site.

Pharmacokinetics

Nevirapine is extensively metabolized in the liver by cytochrome P450 (CYP) isoenzymes 3A4 and 2B6, and is mainly excreted into the urine as glucuronidated and hydroxylated metabolites (80%) and as parent drug (5%).Nevirapine causes induction of its metabolism, resulting in a 1.5- to 2-fold increase in the oral clearance during the first weeks of dosing. The plasma elimination half-life is about 45 h after a single dose, and about 25-30 h during steady-state dosing.The licensed dosage for nevirapine is 200 mg twice-daily, after a starting dose of 200 mg once-daily during the first 2 weeks of therapy.

Absorption and Bioavailability

Nevirapine is readily absorbed (> 90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was 93 ± 9% (mean ± SD) for a 50 mg tablet and 91 ± 8% for an oral solution. Peak plasma nevirapine concentrations of 2 ±

0.4 µg/mL (7.5 µM) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady state trough nevirapine concentrations of 4.5 ± 1.9 µg/mL (17 ± 7 µM), (n = 242) were attained at 400 mg/day

Distribution

Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution (Vdss) of nevirapine was 1.21 ± 0.09 L/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is also found in breast milk.

Metabolism/Elimination

In vivo studies in humans and in vitro studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites.

Drug Interactions

Nevirapine is principally metabolized by the liver via the cytochrome P450 isoenzymes, 3A4 and 2B6. Nevirapine is known to be an inducer of these enzymes. As a result, drugs that are metabolized by these enzyme systems may have lower than expected plasma levels when coadministered with nevirapine. These potential drug interactions are listed in Table No 3.2.

Table No.4.2 Established Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies

Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
Clarithromycin	Clarithromycin 14OH- clarithromycin	Clarithromycin exposure was significantly decreased by nevirapine; however, 14-OH metabolite concentrations were increased.
Ethinyl estradiol and Norethindrone	Ethinyl estradiol Norethindrone	Oral contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking nevirapine,
Fluconazole	Nevirapine	Because of the risk of increased exposure to nevirapine.
Indinavir	Indinavir	An increase in the dosage of indinavir may be required.
Ketoconazole	Ketoconazole	Decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.
Lopinavir/Ritonavir	Lopinavir	A dose increase of lopinavir/ritonavir to 533/133 mg twice daily with food is recommended.
Methadone	Methadone	Methadone levels may be decreased; increased dosages may be required to prevent symptoms of opiate withdrawal.
Rifabutin	Rifabutin	Rifabutin and its metabolite concentrations were moderately increased.

Rifampin	Nevirapine	Nevirapine and rifampin should not administered concomitantly because decreases in nevirapine plasma concentrations may reduce the efficacy of the drug

Side effects

The most serious adverse reactions associated with nevirapine are hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions.

Contraindications

Nevirapine is contraindicated in patients with clinically significant hypersensitivity to any of the components contained in the tablet or the oral suspension.

4.3. EXCIPIENTS SPECIFICATIONS [2]

4.3.1. CROSCARMELLOSE SODIUM

Product Description [63.67]

Ac-Di-Sol is FMC Biopolymer's trademark for an internally cross-linked form of sodium carboxymethylcellulose (NaCMC). Ac-Di-Sol differs from soluble sodium carboxymethylcellulose only in that it has been cross-linked to ensure that the product is essentially water insoluble. It is an odorless, relatively free flowing, white powder.

Description

Croscarmellose sodium occurs as odorless, white-colored powder.

Nonproprietary Names

USPNF: Croscarmellose sodium

Synonyms

Ac-Di-Sol; Crosslinked carboxymethylcellulose sodium; modified cellulose gum; Nymcel ZSX; Primellose; Solutab

Chemical name

Cellulose, Carboxy methyl ether, sodium salt cross linked

Empirical formula and Molecular weight:

Croscarmellose is a cross linked of Carboxy methyl sodium

Applications in Pharmaceutical Formulation or Technology

Croscarmellose sodium is used in oral pharmaceutical formulation as a disintegrant for tablets, capsules and granules.

Stability and Storage conditions

Sodium is a stable though hygroscopic material. Croscarmellose sodium should be stored in a well closed container in a cool, dry place**.**

Incompatibility

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by wet granulation or direct compression processes which contain hygroscopic excipients such as sorbitol.

4.3.2. POLYPLASDONE [62]

Polyplasdone is a synthetic, insoluble, but rapidly swellable, crosslinked homopolymer of N-vinyl-2-pyrrolidone.Polyplasdone polymers are synthesized by a unique one step polymerization process known as "**popcorn**" polymerization where the cross linking agent is generated in situ and is, thus chemically similar to the bulk of the polymer. This unique manufacturing process results in a densely cross linked polymer with porous particle morphology. This distinctive morphology rapidly wicks liquids in to the particle to speed swelling and enhance disintegration and dissolution of tablets. The particle morphology of Polyplasdone polymers also provides for a highly compressible powder with good flow properties that result in hard, non friable tablets.

In addition to its unique particle morphology, Polyplasdone polymers are non ionic and, as a result, their disintegration performance will not be impacted by pH changes in the gastrointestinal tract nor they will complex with ionic drug actives Polyplasdone polymers will not retard the disintegration and dissolution processes since they do not form gels. Consequently, Polyplasdone polymers are well suited for use as superdisintegrants in a wide range of oral solid dosage formulation. In addition to their use as a disintegrant, Polyplasdone polymers can also be used as adsorptive polymers, suspension stabilizers, and for bioavailability enhancement in a variety of pharmaceutical applications.

Polyplasdone crospovidone (NF) products are superdisintegrants with the greatest rate of swelling of any excipient. They are effective in wet granulation, dry granulation and direct compression tablet processing. They are manufactured by a unique process. Unlike most polymeric disintegrants which consist of a natural or semi natural water soluble polymer which is then cross linked chemically, the polymerization and cross-linking occurs simultaneously to yield a controlled insoluble mass. This results in amorphous spherical particles which are then spray dried to produce free flowing compressible powder to enable even distribution and excellent powder flow. The spherical particles unique to Polyplasdone crospovidone superdisintegrants distribute evenly throughout the tablet and have a greater surface area/volume ratio than other disintegrants. This feature, coupled with the amorphous open structure of the particles, result in rapid swelling in all directions in the presence of any physiological fluid. This leads to the rapid development of high internal stresses which cause the tablet to disintegrate.

The fully cross-linked nature of polyplasdone crospovidone means that it is completely insoluble and will not develop any viscosity. This precludes the possibility of delayed disintegration or even sustained release. It also ensures that its full disintegration potential is maintained even after undergoing several wetting/drying cycles.

This mechanism of disintegration is so efficient it renders Polyplasdone XL and Polyplasdone XL-10 effective at concentration levels of typically, 1-3%.Polyplasdone crospovidone can be incorporated at any stage in the pre-tableting process to give required control over the rate of disintegration of both tablet and its component granules. This means one particle size can be used pre-granulation and a different particle size disintegrant post granulation. The smaller particle size product, Polyplasdone XL-10 can be used intragranularly (before granulation) to maximize distribution, while the larger particle size product, Polyplasdone XL, with its stronger disintegration power, is more effective extragranularly. The formulation flexibility and excellent functionality of Polyplasdone crospovidone make it a superdisintegrant of choice.

Product Range:

ISP offers 3 chemically identical Polyplasdone grades differentiated by particle size.

Polyplasdone XL polymer has the largest average particle size (100-130µ) and provides faster disintegration.

Polyplasdone XL 10 has finer average particle sizes (30-50µ) which enhance content uniformity in the formulation of tablets (less than 300mg) and in intragranular applications while still providing rapid disintegration.

Polyplasdone INF -10 polymers has the finest average particle size (5-10µ) of the Polyplasdone grades and is highly adsorptive material.

Product profile

Solubility and Viscosity

- Polyplasdone crospovidone is completely insoluble in water and all solvents as a consequence of its cross-linked structure.
- It swells extremely rapidly in water which makes it the premier superdisintegrants for solid dosage form.

- It is hydrophilic and on contact, rapidly absorbs water. This causes massive build up of hydrostatic pressure which is a key contributor to its disintegration potential
- .It rapidly disperses in water and does not even gel even after prolonged exposure.
- It does not affect the viscosity of water or solvents

Particle characteristics

Polyplasdone crospovidone grades are flowable white powders which are easy to handle on a manufacturing scale. Polyplasdone particles are granular and porous. This unique particle structure allows for improved flow and quick wicking of liquid in to the particle and tablet by capillary action. In addition, this particle morphology contributes to the high compressibility of Polyplasone XL and XL-10 polymers. Although Polyplasdone XL-10 polymer has smaller particles than Polyplasdone XL polymer, the small particles retain their porosity and resulting physical properties.

4.3. Particle characteristics

PRODUCT	PARTICLE SIZE(µM)	TAP DENSITY(G/CM^3)	BULK DENSITY(G/CM^3)	CARR INDEX (%)
Polyplasdone XL	100	0.3	0.2	22
Polyplasdone XL 10	30	0.5	0.3	30
Polyplasdone INF-10	11	0.5	0.4	20

Flow

As Polyplasdone polymers are supplied as free-flowing, white powders, they are easy to handle during direct compression and wet and dry granulation manufacturing processes. Polyplasdone XL and XL-10 polymers have good flow properties which are attributed to their granule particle morphology.

Table No: 4.4 Flow Characteristics

PROPERTY	POLYPLASDONE		
	INF-10	XL-10	XL
Angle of repose(degrees)	41	30	35
Flowability Index	45	50	47

Compressibility

Due to their unique particle morphology, Polyplasdone XL and XL-10 disintegrants are significantly more compressible than other superdisintegrants, resulting in harder, less friable tablets. Polyplasdone XL and XL-10 polymers provide significantly higher hardness of pure compacts. Consequently, Polyplasdone disintegrant is ideally suited for use with poorly compressible actives and in direct compression tablet processes.

Adsorption and complexation

Polyplasdone crospovidone has a high adsorptive capacity and, as well as swelling, complexes with many molecules including some drugs and toxins. This is a reversible physical complexation without formation of covalent chemical bonds.

Swelling and Hydration

Although Polyplasdone XL and XL-10 polymers swell by 95-120%, upon contact with water, swelling is not thought to be their primary mechanism for disintegration. Swelling or swell volume is mainly a measure of the change in the volume of the disintegrant after it is introduced to an aqueous solution and system has reached equilibrium. Polyplasdone polymers with their porous particle morphology rapidly absorb water (wicking) to generate the rapid volume expansion and hydrostatic pressure that cause tablet disintegration. Unlike other superdisintegrants which rely principally on swelling for disintegration, Polyplasdone disintegrants use the combination of swelling and wicking to provide rapid disintegration.

Also, unlike other common superdisintegrants, the swell volume of Polyplasdone polymers is relatively unaffected by changes in pH. As a result of high cross link density, Polyplasdone disintegrants swell without gelling. Other superdisintegrants have a lower crosslink density and, as a result, forms gels when

fully hydrated. Gels can delay dissolution as the drug must first diffuse through the gel layer before being released into the body. Also, because Polyplasdone disintegrants don't gel upon wetting, they will maintain their full disintegration efficacy even after undergoing several wetting and drying cycles. Therefore, polyplasdone disintegrants are ideally suited for use in wet granulation processes.

Applications in pharmaceutical formulations or Technology:

Polyplasdone crospovidone is used in a range of pharmaceutical applications. Polyplasone XL and XL-10 polymers provide rapid disintegration in a wide range of oral solid dosage formulations and processes.

4.3.3. SODIUM STARCH GLYCOLATE [67]

Nonproprietary Names

- BP: Sodium starch glycollate
- PhEur: Carboxymethylamylum natricum
- USPNF: Sodium starch glycolate

Synonyms

Carboxymethyl starch, Sodium salt; Explosol, Explotab, Glycolys, Primojel, Starch Carboxymethyl ether, Sodium salt, Tablo, Vivastar P.

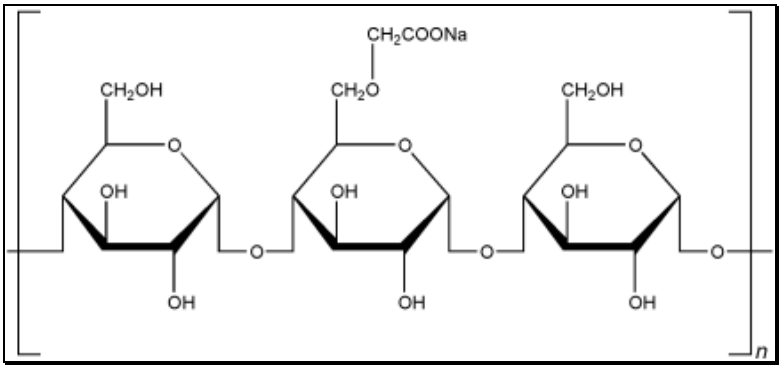
Chemical Name : Sodium carboxymethyl starch

Empirical Formula and Molecular Weight

Sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch, containing 2.8–4.2% sodium.

Sodium starch glycolate may be characterized by the degree of substitution and crosslinking. The molecular weight is typically 5×10^5–1×10^6.

Structural Formula



Functional Category

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.

Description

Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder.

Stability and Storage Conditions

Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

The physical properties of sodium starch glycolate remain unchanged for up to 3–5 years if it is stored at moderate temperatures and humidity.

Incompatibilities

Sodium starch glycolate is incompatible with ascorbic acid.

4.4. DISSOLUTION PROFILE COMPARISON

In the development of oral controlled release preparations, an ethical or proprietary product, which has been available in the market and established its efficacy clinically, is usually selected as reference. The generic preparation is always formulated with its dissolution profile as closely similar as possible to that of proprietary product. Several methods have been proposed to compare the dissolution profiles of test with that of reference. Those methods were classified into several categories, such as:

- Model Dependent Kinetics
- Model Independent Kinetics
- Statistical methods

Model Dependent Methods

The model dependent methods all rely upon a curve fitting procedure. Different mathematical functions have been used to model the observed data (Costa and Sousa Lobo 2001). Both the linear and non-linear models are being used in practice for dissolution modeling. Linear models include Zero order, Higuchi, Hixson-Crowell, quadratics and polynomials, whereas the nonlinear models include First order, Weibull, KorsMeyer-Peppas etc

Model Independent Methods

Model independent methods were now gaining more popularity in pharmaceutical industries to have to compare the dissolution profiles of test and reference, which is required at time of submission to US FDA for approval of generic drugs. Model independent methods to compare the dissolution profiles are again differentiated into ratio tests and pair wise procedures. The ratio tests are relations between parameters obtained from the release assay of the reference formulations and test product at the same time. To compare dissolution profiles ratio tests like Dissolution efficiency (DE), Mean dissolution time (MDT), Time taken to release x% drug (t_x %).

Dissolution Efficiency

The dissolution efficiency (DE) of a pharmaceutical dosage form is defined as the area under dissolution curve up to a certain time, t, expressed as percentage of the area of the rectangle described by 100% dissolution in the same time**.**

$$DE = \frac{\int_0^t y.dt}{y_{100}.t} \times 100\% \quad \text{(Khan KA, 1975)}^{20}$$

Mean Dissolution Time

The mean Dissolution Time is defined as the time required by the dosage form to dissolve the 50% of the drug**.**

Time taken to release x% drug:

The t_x % parameter corresponds to the time necessary to the release of a determined percentage of drug (e.g., t_{20}%, t_{50}%, t_{80}%) and sampling time corresponds to the amount of drug dissolved in that time (e.g., t_{20}, t_{50}, t_{80}).

5. EXPERIMENT

5.1. Instruments

Table No: 5.1 List of Instruments

Instrument	Source
Granulator	Bectochem
Moisture content	Sartorius Moisture Balance
Compression of tablet	CADMACH Square model single sided Rotary tablet press CMD4 , Ahmedabad
Hardness Tester	Erweka TBH 310 MD, Germany
Friabilator	Erweka, Germany
Disintegration Apparatus	Erweka, Germany
UV-Spectrophotometer	8453 Agilent Technologies, Germany
Dissolution Apparatus	VK 7010 Varian
Sonicator	Cole Parmer 8890
Electronic balance	Sartorius
pH Meter	744 Metrohm
Stability Chamber	Pooja Labs

5.2. Formulation and Development

General Formula

Table No: 5.2 The general formula of Efavirenz (600mg) tablets prepared were as follows

S.NO.	Ingredients	Control	Quantity in mg/tablet
1.	Efavirenz	600	600
2.	MCC pH 101	254	204
3.	Lactose Monohydrate	250	240
4.	Sodium Lauryl Sulphate	36	36
5.	Plasdone K29/32	36	36
6.	Superdisintegrants	-	60
7.	Magnesium Stearate	12	12
8.	Aerosil	12	12
Total		**1200**	**1200**

Table No: 5.3 The general formula of Acyclovir (800mg) tablets prepared were as follows

S.NO.	Ingredients	Control	Quantity in mg/tablet
1.	Acyclovir	800	800
2.	MCC pH 101	640	565
5.	Plasdone K29/32	45	45
6.	Superdisintegrants	-	75
7.	Magnesium Stearate	10	10
8.	Aerosil	5	5
Total		**1500**	**1500**

Table No: 5.4 The general formula of Nevirapine (200mg) tablets prepared were as follows

S.NO.	Ingredients	Control	Quantity in mg/tablet
1.	Nevirapine	200	200
2.	MCC pH 101	305	265
3.	Lactose Monohydrate	302.5	300
5.	Plasdone K29/32	25.5	25.5
6.	Superdisintegrants	-	42.5
7.	Magnesium Stearate	8.5	8.5
8.	Aerosil	8.5	8.5
Total		**850**	**850**

Codes

Efavirenz	EF
Acyclovir	AC
Nevirapine	NE
Crosscarmellose Sodium	T_1
Sodium Starch Glycolate	T_2
Polyplasdone XL	T_3
Polyplasdone XL10	T_4

Table No: 5.5 Batch Codes

S.NO.	Superdisintegrants	Efavirenz 600mg	Acyclovir 800mg	Nevirapine 200mg
1.	Crosscarmellose Sodium	EFT_1	ACT_1	NET_1
2.	Sodium Starch Glycolate	EFT_2	ACT_2	NET_2
3.	Polyplasdone XL	EFT_3	ACT_3	NET_3
4.	Polyplasdone XL10	EFT_4	ACT_4	NET_4

5.3. Compression Technique

Efavirenz (600mg)

The required quantities of the ingredients (Efavirenz, MCC pH 101, Lactose Monohydrate, Plasdone K29/32, and SLS) were weighed and blended to form a homogenous powder by sieve number 30. Then the prepared blends were granulated by using procept granulator with water. The wet granules were dried in air drying. After drying it was sieved under sieve number 24. The lubricants were sieved under sieve number 30 and mixed well. The granules were compressed on 19mm and 9mm capsule shaped punch set on Rotary Compression Machine (CAD MACH) at 1200mg theoretically weighed and at approximately equal hardness. The compression and ejection force simultaneously recorded by AIM software.

Acyclovir (800mg)

The required quantities of the ingredients (Acyclovir, MCC pH 101) were weighed and blended to form a homogenous powder by sieve number 30. Plasdone K29/32 was dissolved in water at 10% w/v. Then the prepared blends were granulated by using procept granulator with polyplasdone K29/32 solution. The wet granules were dried in air drying. After drying it was sieved under sieve number 24. The lubricants were sieved under sieve number 30 and mixed well. The granules were compressed on 19mm and 9mm capsule shaped punch set on Rotary Compression Machine (CAD MACH) at 1500mg theoretically weighed and at approximately equal hardness. The compression and ejection force simultaneously recorded by AIM software.

Nevirapine (200mg)

The required quantities of the ingredients (Nevirapine, MCC pH 101, Lactose Monohydrate) were weighed and blended to form a homogenous powder by sieve number 30. Plasdone K29/32 was dissolved in water at 10% w/v. Then the prepared blends were granulated by using procept granulator with polyplasdone K29/32 solution. The wet granules were dried in air drying. After drying it was sieved under sieve number 24. The lubricants were sieved under sieve number 30 and mixed well. The granules were compressed on 19mm and 9mm capsule shaped punch set on Rotary Compression Machine (CAD MACH) at 1500mg theoretically weighed and at approximately equal hardness. The compression and ejection force simultaneously recorded by AIM software.

Preparation of Granules Using Procept High Shear Granulator

The mixing vessel of granulator was charged with drug mixture and pre mixed at an impeller speed of 1000rpm for 60sec.Water was added at a pre-determined rate and after 120sec chopper was started at 2500rpm and granulation performed. The impeller torque and product temperature are monitored to determine the end point of granulation. Granules sieved through 30 meshes and dried to a final moisture content of 1.5-2%w/w (determined using sartorius moisture balance).

5.4. Evaluation Techniques

Evaluation of Granules

A. Bulk Density, Tapped Density and Compressibility

Bulk density was measured by tapping method**.**

$$\text{Bulk Density} = \frac{\text{Mass of the sample}}{\text{Volume of the measuring cylinder}}$$

An automated tap density tester (Procept Density apparatus) was used for tapping the powders according to USP Method. In brief, the graduated cylinder was mounted on the tap density tester. The powders were filled into the cylinder using a funnel, and the volume and weight were recorded to calculate the bulk density. The apparatus was tapped for 100 times. The volume was recorded, and the tapped density was calculated.

$$\text{Tapped Density} = \frac{\text{Mass of the sample}}{\text{Volume of the measuring cylinder after tapping}}$$

$$\text{Compressibility (\%)} = (p_{tap} - p_{bul}) / p_{tap} \times 100$$

where p_{tap} is the tapped bulk density and p_{bul} is the initial bulk density.

B. Drug Content Uniformity of Granules

For Efavirenz

Accurately weighed granules of equivalent to 600mg of drug were taken in a 500ml volumetric flask. Then 20 to 30ml of methanol was added to dissolved, and then made the volume by using 2% SLS medium. It was filtered. From that 1ml was taken in a 100ml volumetric flask and made the volume by using 2% SLS medium (12µg/ml). Then the drug content was analyzed by using UV Visible Spectrophotometer (Agilent UV-Spectrophotometer at 247 nm and compared with the standard. Accurately weighed 600mg pure drug efavirenz was taken in the similar manner. The percentage of drug present in the granules was calculated by the following equation

$$\text{The percentage of drug content} = \frac{\text{Observed drug content}}{\text{Theoretical drug content}} \times 100$$

For Acyclovir

The above same method was followed and the granules weight was 800mg equivalent was taken. Media was 0.1N HCl and measured at 251nm (16µg/ml).

For Nevirapine

Accurately weighed granules of equivalent to 200mg of granules were taken in a 200ml volumetric flask. Then 20 to 30ml of dimethyl sulphoxide (DMSO) was added to dissolved, and then made the volume by using pH 2 Phosphate buffer medium. It was filtered. From that 2ml was taken in a 100ml volumetric flask and made the volume by using pH 2 Phosphate buffer medium (20µg/ml). Then the drug content was analyzed by using UV Visible Spectrophotometer (Agilent UV-Spectrophotometer at 314 nm and compared with the standard. Accurately weighed 200mg pure drug nevirapine was taken in the similar manner. The percentage of drug present in the granules was calculated by the above same method.

C. Moisture determination for granules:

The granulation moisture content was determined using Sartorius moisture balance. An amount of 1 g of wet granules were exposed for 3 min in quick drying mode at 105ºC and percentage of moisture was noted for each case.

Evaluation of Tablets

A. Weight variation test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Sartorius), and test was performed according to the official method.

B. Hardness

For each formulation, the hardness of 10 tablets was determined using Erweka hardness tester and average is calculated and presented with standard deviation

C. Friability

A sample of 20 tablets was taken and was carefully dedusted prior to testing. The tablets were accurately weighed and placed in drum of the Roche Friabilator

(Erweka, Germany), and the drum was rotated for 4min at 25rpm, and tablets were removed, dedusted and accurately weighed.

Friability of tablets is calculated by using the following relationship

$$\%F = W_0 - W_f / W_0 \times 100$$

Where W_0 is the initial weight of 20 tablets and W_f is the final weight of 20 tablets.

D. Disintegration test

Disintegration testing was performed at 37ºC in Millipore water using Erweka apparatus (Germany) with disks. The test was carried out as per USP and averages of 6 readings were recorded for each formulation.

E. Drug content uniformity of tablets

For Efavirenz

20 tablets were weighed and made powder by crushing the tablets, from that weighed equivalent to 600mg of the drug placed in 500ml beaker. Then 20 to 30ml of methanol added to dissolve the drug then made the volume by using medium 2% SLS. It was filtered. From that 1ml was taken in a 100ml volumetric flask and made the volume by using 2% SLS medium (12µg/ml). After graded dilution the drug solution was analyzed in spectrophotometer (Agilent UV-Spectrophotometer) at 247nm then compared to standard. The percentage of drug present in the tablets were calculated by the following equation

$$\text{The percentage of drug content} = \frac{\text{Observed drug content}}{\text{Theoretical drug content}} \times 100$$

The above same method was followed and the tablet crushed weight was 800mg equivalent was taken. Media was 0.1N HCl and measured at 251nm (16µg/ml).

For Nevirapine

20 tablets were weighed and made powder by crushing the tablets, from that weighed equivalent to 600mg of the drug placed in 200ml beaker. Then 20 to 30ml of dimethyl sulphoxide (DMSO) added to dissolve the drug then made the volume by using pH 2 Phosphate buffer medium. It was filtered. From that 2ml was taken in a 100ml volumetric flask and made the volume by using pH 2 Phosphate buffer medium (20µg/ml). After graded dilution the drug solution was analyzed in spectrophotometer (Agilent UV-Spectrophotometer) at 314nm then compared to standard. The percentage of drug present in the granules was calculated by the above same method.

F. Moisture determination for tablets:

One compressed tablet was crushed in a mortar and pestle. The granulation moisture content was determined using Sartorius moisture balance. An amount of 1 g of granules were exposed for 3 min in quick drying mode at 105ºC and percentage of moisture was noted for each case.

G. Analytical Methods

For Efavirenz

Preparation of 2% SLS in water

100 grams of SLS was dissolved in 5 liters of Millipore water and made the volume to 5 liters.

Preparation of Standard Calibration Curve in 2% SLS in water

Accurately weighed 100 mg of pure drug were transferred to 250 ml volumetric flask and were dissolved in methanol with sonication. The volume was made up to 250 ml by using medium (2% SLS in water). From this withdraw 1ml, 2ml, 3ml, 4ml and 5ml placed in 100ml flask and then made up to 100ml with same medium from this graded dilution in the concentration range of 4.0 to 20.0 µg/ml were prepared. Before going for spectroscopic analysis drug solution was scanned for λmax. The λmax was found to be 247 nm in buffer. Then absorbance of prepared standard solution was measured and plotted against concentration. Regression analysis has been done and standard curve was plotted to get correlation factor = 0.999.

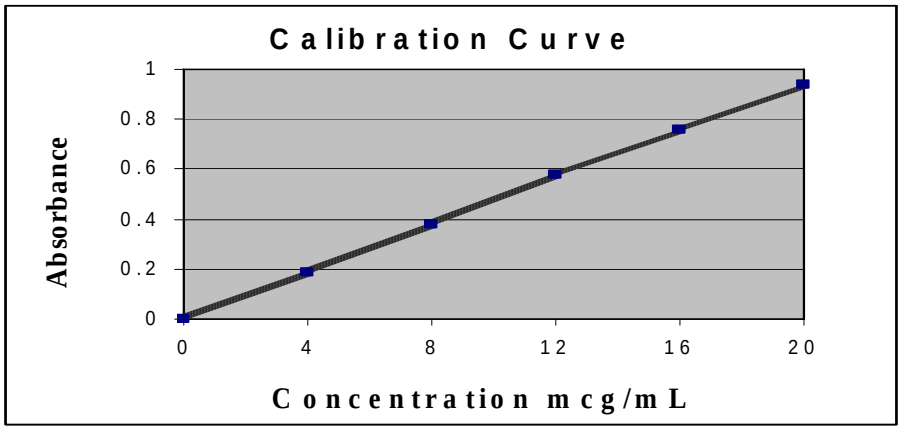


Fig No: 5.1 Graph of Standard Calibration Curve in 2% SLS in water

Table No: 5.6 Data of Standard Calibration Curve in 2% SLS in water

S.NO.	CONCENTRATION IN mcg/ml	ABSORBANCE
1.	4.0	0.18727
2.	8.0	0.37974
3.	12.0	0.57549
4.	16.0	0.75876
5.	20.0	0.93951

Preparation of 0.2% SLS in water

10 grams of SLS were dissolved in 5 liters of Millipore water and made the volume to 5 liters.

Preparation of Standard Calibration Curve in 0.2% SLS in water

Accurately weighed 100 mg of pure drug were transferred to 250 ml volumetric flask and were dissolved in methanol with sonication. The volume was made up to 250ml by using medium (0.2% SLS in water). From this withdraw 1ml, 2ml, 3ml, 4ml, 5ml and 10ml placed in 100ml flask and then made up to 100ml with same medium from this graded dilution in the concentration range of 4.0 to 30.0 µg/ml were prepared. Before going for spectroscopic analysis drug solution was scanned for λmax. The λmax was found to be 247 nm in buffer. Then absorbance of prepared standard solution was measured and plotted against concentration. Regression analysis has been done and standard curve was plotted to get correlation factor = 0.999.

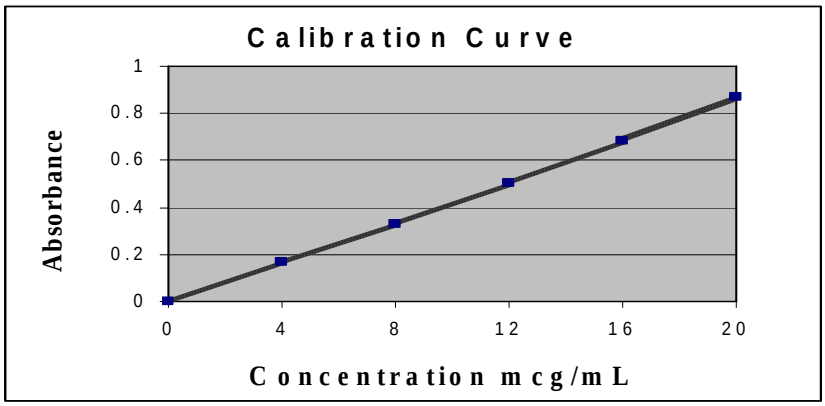


Fig No: 5.2 Graph of Standard Calibration Curve in 0.2% SLS in water

Table No: 5.7 Data of Standard Calibration Curve in 0.2% SLS in water

S.NO.	CONCENTRATION IN mcg/ml	ABSORBANCE
1.	4.0	0.16644
2.	8.0	0.32759
3.	12.0	0.50564
4.	16.0	0.68544
5.	20.0	0.87136

Dissolution Parameters

The tablets were subjected to in-vitro dissolution profiling using Varian dissolution apparatus. The dissolution profiles of the Efavirenz-600mg tablets were determined using the paddle method (Varian) set with a paddle speed of 50 rpm. Dissolution was als 5to tested in two media i.e. 1000ml water with 2% SLS (compendia media, USP), 1000ml Water with 0.2% SLS (quasi-sink media). A peristaltic pump was coupled to an Auto sampler to provide a continuous flow of drug solution through the test tubes. Samples were withdrawn at 5, 10, 15, 30, 45 and 60 minutes interval, diluted suitably and analyzed for drug content using UV-Visible spectrophotometer (Agilent Technologies) at λ_{max} = 247 nm. The data given were the mean of 6 determinations.

For Acyclovir

Preparation of 0.1N HCl

170ml of Concentrated Hydrochloric acid was taken in a beaker containing 3 liters of water and made the volume up to 20 liters.

Preparation of Standard Calibration Curve for 0.1N HCl

Accurately weighed 100 mg of pure drug were transferred to 250 ml volumetric flask and were dissolved in methanol with sonication. The volume was made up to 250 ml by using medium (0.1N HCl). From this withdraw 1ml, 2ml, 3ml, 4ml and 5ml placed in 100ml volumetric flask and then made up to 100ml with same medium from this graded dilution in the concentration range of 4.0 to 20.0 µg/ml were prepared. Before going for spectroscopic analysis drug solution was scanned for λmax. The λmax was found to be 251 nm in buffer. Then absorbance of prepared standard solution was measured and plotted against concentration. Regression analysis has been done and standard curve was plotted to get correlation factor = 0.999.

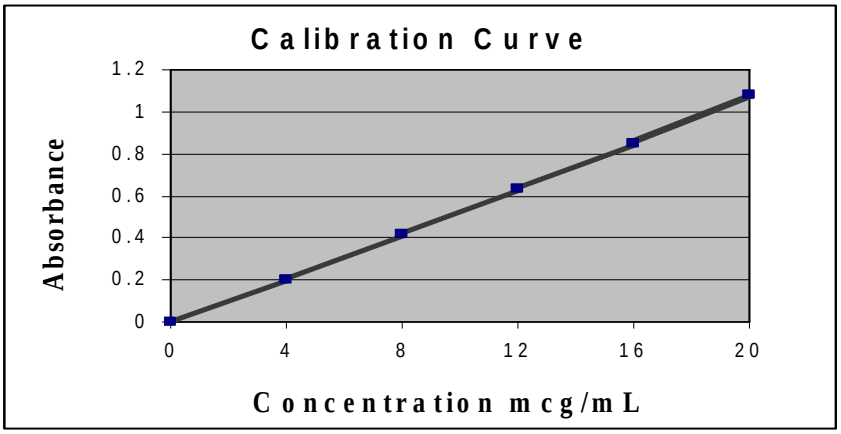


Fig No: 5.3 Graph of Standard Calibration Curve for 0.1N HCl

Table No: 5.8 Data of Standard Calibration Curve for 0.1N HCl

S.NO.	CONCENTRATION IN mcg/ml	ABSORBANCE
1.	4.0	0.20160
2.	8.0	0.41606
3.	12.0	0.63375
4.	16.0	0.84775
5.	20.0	1.07800

Dissolution Parameters

The tablets were subjected to in-vitro dissolution profiling using Varian dissolution apparatus. The dissolution profiles of the Acyclovir-800mg tablets were determined using the paddle method (Varian) set with a paddle speed of 50 rpm. Dissolution was also tested in two media i.e. 900ml 0.1N HCl(compendia media, USP), 500ml 0.1N HCl (quasi-sink media). A peristaltic pump was coupled to an Auto sampler to provide a continuous flow of drug solution through the test tubes. Samples were withdrawn at 5, 10, 15, 30, 45 and 60 minutes interval, diluted suitably and analyzed for drug content using UV-Visible spectrophotometer (Agilent Technologies) at λ_{max} = 251 nm. The data given were the mean of 6 determinations.

For Nevirapine

Preparation of 0.1M pH 2 Phosphate Buffer

3.9ml concentrated phosphoric acid and 5.73G of monobasic sodium phosphate monohydrate to a 1 liter volumetric flask, dissolve and dilute with water to volume, adjust pH 2.0 ± 0.02.

Preparation of Standard Calibration Curve for 0.1M pH 2 Phosphate Buffer

Accurately weighed 100 mg of pure drug were transferred to 250 ml volumetric flask and were dissolved in dimethyl sulphoxide (DMSO) with sonication. The volume was made up to 250 ml by using medium 0.1M pH 2 Phosphate Buffer. From this withdraw 1ml, 2ml, 3ml, 4ml and 5ml placed in 100ml volumetric flask and then made up to 100ml with same medium from this graded dilution in the concentration range of 4.0 to 20.0 µg/ml were prepared. Before going for spectroscopic analysis drug solution was scanned for λmax. The λmax was found to be 314 nm in buffer. Then absorbance of prepared standard solution was measured and plotted against concentration. Regression analysis has been done and standard curve was plotted to get correlation factor = 0.999.

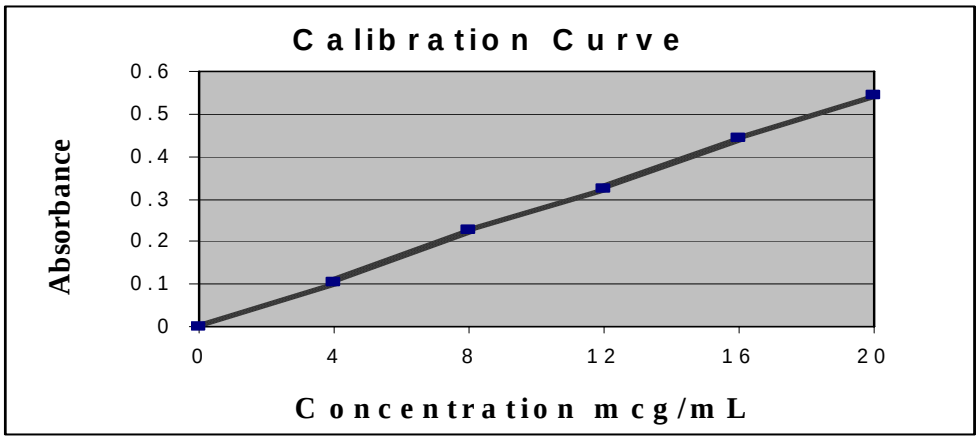


Fig No: 5.4 Graph of Standard Calibration Curve for 0.1M pH 2 Phosphate Buffer

Table No: 5.9 Data of Standard Calibration Curve for 0.1M pH 2 Phosphate Buffer

S.NO.	CONCENTRATION IN mcg/ml	ABSORBANCE
1.	4.0	0.10283
2.	8.0	0.22654
3.	12.0	0.32451
4.	16.0	0.44268
5.	20.0	0.54277

Dissolution Parameters

The tablets were subjected to in-vitro dissolution profiling using Varian dissolution apparatus. The dissolution profiles of the Nevirapine-200mg tablets were determined using the paddle method (Varian) set with a paddle speed of 50 rpm. Dissolution was also tested in two media i.e. 900ml 0.1M pH 2 Phosphate Buffer (compendia media, USP), 500ml 0.1M pH 2 Phosphate Buffer (quasi-sink media). A peristaltic pump was coupled to an Auto sampler to provide a continuous flow of drug solution through the test tubes. Samples were withdrawn at 5, 10, 15, 30, 45 and 60 minutes interval, diluted suitably and analyzed for drug content using UV-Visible spectrophotometer (Agilent Technologies) at λ_{max} = 314 nm. The data given were the mean of 6 determinations.

Stability Studies

The prepared tablets were placed in plastic screw guage containers and stored at a different temperature conditions, 25ºC/60%RH, 30ºC/65%RH and 40ºC/75%RH according to ICH Guidelines, for a period of three months. The tablets were examined for their physical parameters and dissolution comparison at regular intervals of 30days, 60days and 90days.

6. RESULTS AND DISCUSSIONS

The present study is to understand the effect of superdisintegrants in tablet formulations of three poorly soluble anti-viral drugs. According to these study Polyplasdone XL-10 crospovidone displayed obvious differences in three various parameters.

Physical Parameters

In physical parameters, all the trials passes the test and within the limits of Pharmacopoeia. The physical parameters data were showed in Table No: 6.1 to 6.7, 6.8 to 6.14 and 6.15 to 6.21.

In the Disintegration time for Efavirenz, Polyplasdone XL-10 crospovidone is equal with innovator disintegrant croscarmelose sodium (Ac-di-sol), (Ac-di-sol) showed 5 mins 50 secs, whereas Polyplasdone XL-10 crospovidone was showed 7 mins 50 secs.

In acyclovir, Polyplasdone XL crospovidone was first disintegrated at 3 mins 28 secs, next is Polyplasdone XL-10 crospovidone at 5 mins 24 secs.

In nevirapine, Polyplasdone XL-10 crospovidone was first disintegrated at within 9 secs compared with other superdintegrants used in this study.

The Particle Size distribution of excipients is of considerable importance when formulating tablets. Polyplasdone XL-10 crospovidone has a finer Particle Size distribution which improves mixing and minimizes changes in swelling properties and on the tablet surface resulting from atmospheric humidity**.** The above features Polyplasdone XL-10 crospovidone has recommended as a high performance disintegrant in tablet formulation.

In vitro Drug Release Study

The release data for all the batches of three antiviral drugs are presented in Fig No:6.1, 6.2, 6.3, 6.4, 6.5 and 6.6.

For Efavirenz

In both the media (Compendia medium and Quasi-sink medium) Polyplasdone XL-10 crospovidone showed faster release than Polyplasdone XL10 crospovidone and Croscarmellose Sodium. According to T_{50} and T_{80} data showed in Table No: 6.22 and Fig No: 6.7, 6.8, Polyplasdone XL-10 crospovidone showed faster release

compared to other superdisintegrants used in this study. However, in the Quasi-sink medium (Compromised Sink Condition) none of the disintegrants achieved 80% release. But the tablets with Polyplasdone XL-10 crospovidone showed almost 70% release, which was significantly higher than any of the other disintegrants used.

For Acyclovir

In the compendia medium, Polyplasdone XL-10 crospovidone and Sodium Starch Glycolate (SSG) were comparable and showed faster release than Polyplasdone XL10 crospovidone and croscarmellose Sodium. According to T_{50} and T_{80} data showed in Table No: 6.23 and Fig No: 6.9, 6.10. However, the Quasi-sink was able to discriminate between the different disintegrants, and tablets containing Polyplasdone XL-10 crospovidone showed significantly faster release than any of the disintegrants.

For Nevirapine

According to T_{50} and T_{80} data showed in Table No: 6.24 and Fig No: 6.11, 6.12, Polyplasdone XL-10 crospovidone, showed faster release compared to other disintegrants used in this study in both the Compendia medium and Quasi-sink medium. However, in both the medium Polyplasdone XL-10 crospovidone showed faster release than other disintegrants used in this study. However this was more significantly apparent in the Quasi-sink medium.

Polyplasdone XL-10 crospovidone is a synthetic insoluble, but rapidly swellable, cross-linked polymer. This distinctive morphology rapidly wicks into the particle to speed swelling and enhance disintegration and dissolution of tablets. The particle morphology it provides for a highly compressible powder with good flow properties that result in hard, non friable tablets. In addition, Polyplasdone XL-10 crospovidone are non-ionic, they do not form gels, will not retard the disintegration and dissolution processes.

T_{50} and T_{80} values was selected because of according to U.S. Pharmacopoeia, and showed a significant difference in to the formulations.

Quasi-sink medium was selected for the dissolution studies, because can not discriminate between the release rates in the Sink conditions. The release rate equal to that 80% was selected, from that in which medium giving 80% release for that drug is selected for Quasi-sink i.e. Compromised Sink Condition. From this Polyplasdone XL-10 crospovidone showed to discriminate between the different disintegrants used in this study.

Dissolution Efficiency

In DE_{30} were showed for all the batches of the model drugs in Fig No: 6.13, 6.14, 6.15. Compared with other disintegrants Polyplasdone XL-10 crospovidone was showed major difference in the DE_{30}. Especially in the model drugs- Acyclovir and Nevirapine, Polyplasdone XL-10 crospovidone were having high DE_{30}.

Stability Studies

Stability studies for all the batches of the model drugs for three different temperature and humidity conditions for the period of three months, there was no significant difference in the physical parameters and in vitro dissolution studies showed in Table No: 6.25, 6.26, 6.27 and Fig No: 6.16 to 6.18, 6.19 to 6.21, 6.22 to 6.24, 6.25 to 6.27, 6.28 to 6.30 and 6.31 to 6.33.

During Storage at a fairly high relative humidity, tablets can be softer and their tensile strength was reduced. Polyplasdone XL and XL-10 crospovidone are insoluble in water due to its cross-linked structures and hygroscopic nature; the final finished products must be protected from atmosphere humidity having excellent stability with no changes in the important product parameters. From that it is concluded that the developed formulations were stable in that stability conditions according to ICH Guidelines.

For Efavirenz (600mg)

Table No: 6.1 Physical Parameters

Physical Parameters	Batches				
	Control	**EFT_1**	**EFT_2**	**EFT_3**	**EFT_4**
Appearance	White, capsule Shaped				
LOD for granules %L	1.65	1.52	1.62	1.72	1.68
Bulk Density (wt/ml)	0.5612	0.5536	0.5542	0.5567	0.5540
Tapped Density (wt/ml)	0.6254	0.6290	0.6180	0.6322	0.6285
% Compressibility	10.27	11.99	10.32	11.94	11.85
Assay 1of granules (%)	99.89	101.06	101.02	99.18	100.12

Table No: 6.2 Weight Variation (gm)

DAYS	Stability Conditions	CONTROL	EFT1	EFT2	EFT3	EFT4
1st	NA	1.2174± 0.014	1.2071± 0.004	1.208± 0.003	1.2101 ± 0.003	1.2069 ± 0.0018
30	25ºC/60%RH	1.2071± 0.003	1.2058± 0.004	1.2041 ± 0.003	1.2072 ± 0.004	1.2063 ± 0.002
30	30ºC/65%RH	1.2172± 0.002	1.2025± 0.001	1.2024 ± 0.008	1.2069 ± 0.002	1.2051 ± 0.002
30	40ºC/75%RH	1.2102± 0.003	1.2055± 0.004	1.2063 ± 0.003	1.2063 ± 0.003	1.2049 ± 0.003
60	25ºC/60%RH	1.2094± 0.02	1.2046± 0.003	1.207± 0.002	1.2067 ± 0.001	1.2047 ± 0.001
60	30ºC/65%RH	1.2082± 0.12	1.2059± 0.002	1.2054 ± 0.001	1.2051 ± 0.003	1.2056 ± 0.002
60	40ºC/75%RH	1.2094± 0.14	1.2065± 0.003	1.2021 ± 0.0006	1.2047 ± 0.005	1.2049 ± 0.003
90	25ºC/60%RH	1.2086± 0.26	1.2061± 0.002	1.2065 ± 0.002	1.2058 ± 0.001	1.2065 ± 0.001
90	30ºC/65%RH	1.2072± 0.32	1.2063± 0.002	1.2064 ± 0.002	1.2070 ± 0.002	1.2067 ± 0.002
90	40ºC/75%RH	1.2064± 0.01	1.2076± 0.001	1.2062 ± 0.002	1.2061 ± 0.002	1.2057 ± 0.002

n=20, Mean ± S

Table No: 6.3 Hardness (N)

DAYS	Stability Conditions	CONTROL	EFT1	EFT2	EFT3	EFT4
1st	NA	113±0.35	143± 0.25	131± 0.58	122± 0.25	131± 0.58
30	25ºC/60%RH	115±0.38	114± 0.37	119± 0.2	113± 0.25	124± 0.37
30	30ºC/65%RH	125±0.42	113± 0.25	122± 0.2	114± 0.2	118± 0.25
30	40ºC/75%RH	148±0.37	113± 0.4	116± 0.37	116± 0.2	114± 0.37
60	25ºC/60%RH	126±0.26	120± 0.55	120± 0.32	116± 0.37	122± 0.25
60	30ºC/65%RH	131±0.34	115± 0.32	124± 0.37	121± 0.58	121± 0.37
60	40ºC/75%RH	141±0.38	118± 0.4	117± 0.51	119± 0.37	120± 0.32
90	25ºC/60%RH	126±0.28	122± 0.24	126± 0.37	119± 0.74	124± 0.49
90	30ºC/65%RH	135±0.34	123± 0.25	123± 0.51	117± 0.25	118± 0.25
90	40ºC/75%RH	141±0.84	119± 0.37	121± 0.37	119± 0.27	120±0. 32

n=10, Mean ± S.D

Table No: 6.4 Friability (%)

DAYS	Stability Conditions	CONTROL	EFT1	EFT2	EFT3	EFT4
1st	NA	0.218	0.215	0.216	0.482	0.166
30	25ºC/60%RH	0.158	0.135	0.391	0.258	0.251
30	30ºC/65%RH	0.068	0.161	0.089	0.139	0.58
30	40ºC/75%RH	0.125	0.164	0.19	0.076	0.122
60	25ºC/60%RH	0.054	0.053	0.103	0.093	0.092
60	30ºC/65%RH	0.152	0.028	0.009	0.098	0.101
60	40ºC/75%RH	0.067	0.159	0.094	0.096	0.053
90	25ºC/60%RH	0.215	0.154	0.04	0.017	0.083
90	30ºC/65%RH	0.158	0.166	0.094	0.098	0.081
90	40ºC/75%RH	0.216	0.076	0.099	0.091	0.081

Table No: 6.5 Disintegration Time (min.)

DAYS	Stability Conditions	CONTROL	EFT1	EFT2	EFT3	EFT4
1st	NA	18.06±0.4	5.17±0.5	16.10±0.8	8.02±0.6	7.50±0.8
30	25ºC/60%RH	18.37±02	5.37±0.3	15.59±0.7	9.13±0.8	7.44±0.6
30	30ºC/65%RH	19.38±0.1	2.50±0.4	17.48±0.4	8.40±0.2	7.23±0.5
30	40ºC/75%RH	19.12±0.12	3.49±0.1	17.43±0.2	8.40±0.1	7.52±0.15
60	25ºC/60%RH	17.12±0.14	5.58±0.2	16.43±0.3	10.03±0.2	8.08±0.4
60	30ºC/65%RH	17.18±0.24	3.18±0.2	17.56±0.1	9.04±0.1	8.17±0.2
60	40ºC/75%RH	17.56±0.34	3.57±0.2	17.56±0.2	8.54±0.2	7.53±0.1
90	25ºC/60%RH	18.18±0.24	6.03±0.3	16.57±0.4	10.16±0.5	8.13±0.2
90	30ºC/65%RH	19.12±0.28	4.04±0.1	17.55±0.3	9.05±0.06	8.56±0.1
90	40ºC/75%RH	18.12±0.29	4.18±0.3	17.54±0.2	9.04±0.05	9.01±0.2

n=6, Mean ± S.D

Table No: 6.6 LOD for Tablets % L

DAYS	Stability Conditions	CONTROL	EFT1	EFT2	EFT3	EFT4
1st	NA	1.89	1.69	1.71	1.57	1.50
30	25ºC/60%RH	2.15	1.89	1.98	1.98	1.98
30	30ºC/65%RH	2.36	1.96	2.45	1.96	2.15
30	40ºC/75%RH	1.89	2.35	2.15	1.64	2.26
60	25ºC/60%RH	1.58	2.15	2.15	2.18	1.95
60	30ºC/65%RH	2.06	2.25	2.16	1.96	1.86
60	40ºC/75%RH	2.25	2.36	2.11	1.65	1.85
90	25ºC/60%RH	2.12	2.18	1.95	2.16	2.10
90	30ºC/65%RH	1.98	1.96	2.11	2.18	2.26
90	40ºC/75%RH	1.65	1.98	2.34	2.17	2.23

Table No: 6.7 Assay for Tablets (%)

DAYS	Stability Conditions	CONTROL	EFT1	EFT2	EFT3	EFT4
1st	NA	98.65	99.18	100.18	98.10	99.68
30	25ºC/60%RH	97.05	99.07	98.08	99.07	99.07
30	30ºC/65%RH	97.26	98.08	99.12	98.12	99.07
30	40ºC/75%RH	96.23	98.07	99.14	98.22	98.12
60	25ºC/60%RH	96.52	98.08	97.12	99.12	99.12
60	30ºC/65%RH	96.32	99.98	98.14	99.72	99.84
60	40ºC/75%RH	97.23	98.12	98.19	99.14	98.12
90	25ºC/60%RH	98.12	97.09	98.14	98.12	98.14
90	30ºC/65%RH	98.12	99.08	99.12	97.14	98.12
90	40ºC/75%RH	98.21	97.02	98.76	99.18	99.14

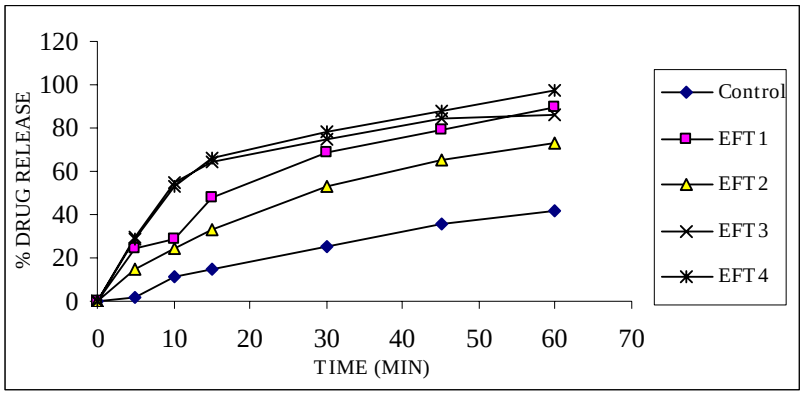


FIG NO: 6.1 COMPARATIVE DISSOLUTION PROFILE OF EFAVIRENZ 600mg AT 50 rpm IN 1000ml WATER WITH 2% SLS (COMPENDIA MEDIUM) ON 1st DAY

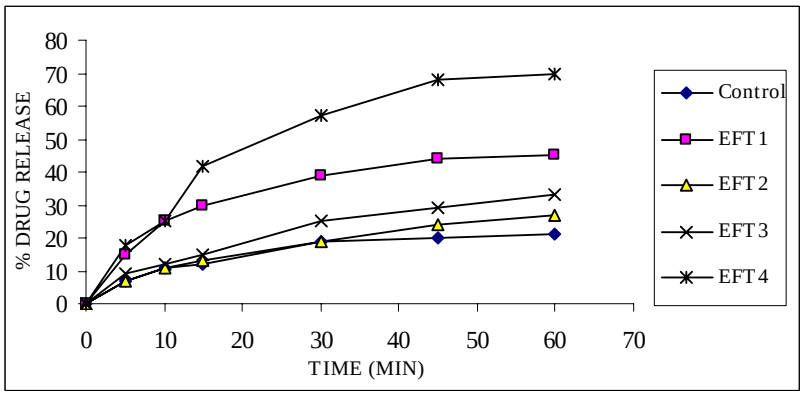
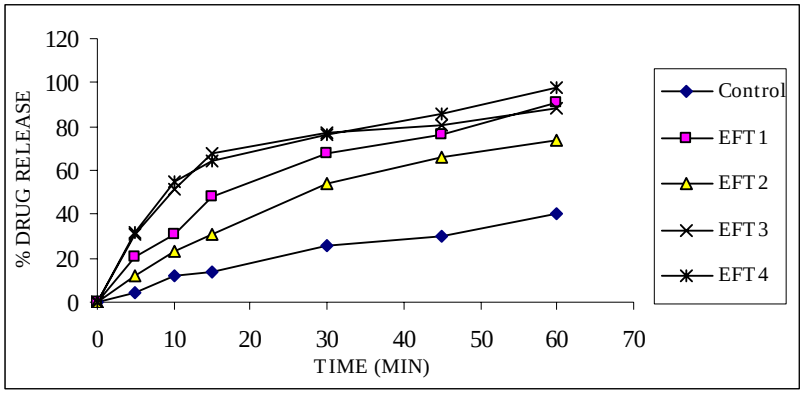
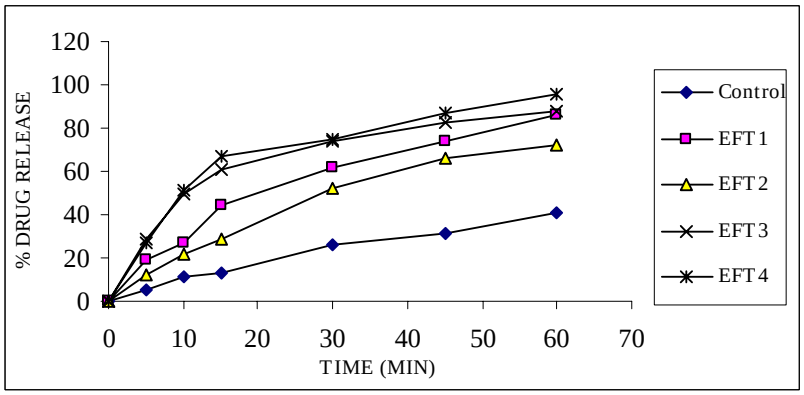


FIG NO: 6.2 COMPARATIVE DISSOLUTION PROFILE OF EFAVIRENZ 600mg AT 50 rpm IN 1000 ml WATER WITH 0.2% SLS (QUASI SINK MEDIUM) ON 1st DAY

25ºC/60%RH



30ºC-65%RH



40ºC-75%RH

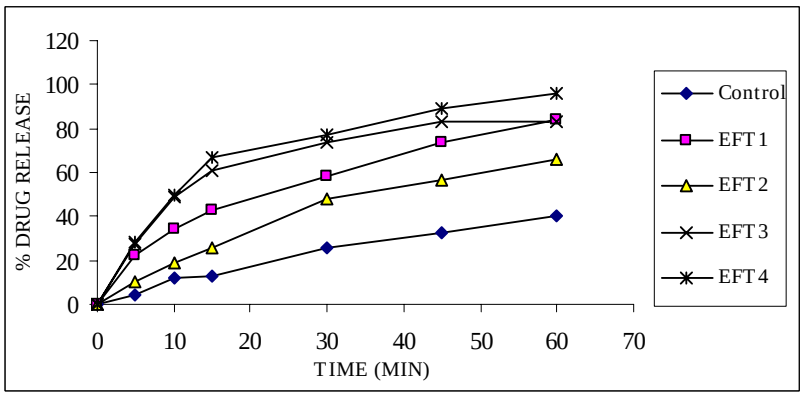
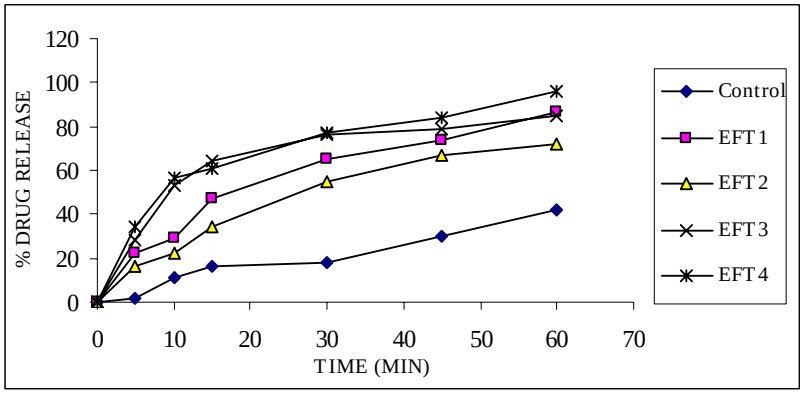
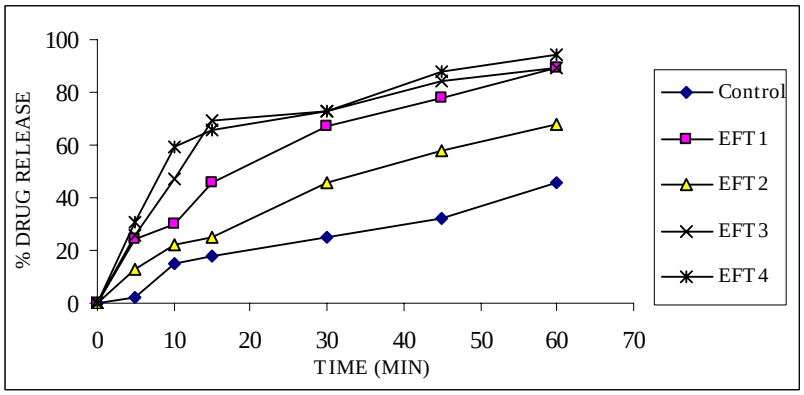


FIG NO: 6.16 COMPARATIVE DISSOLUTION PROFILE OF EFAVIRENZ 600mg AT 50 rpm IN 1000ml WATER WITH 0.2% SLS 30th DAY STABILITY ANALYSIS

25ºC/60%RH



30ºC-65%RH



40ºC-75%RH

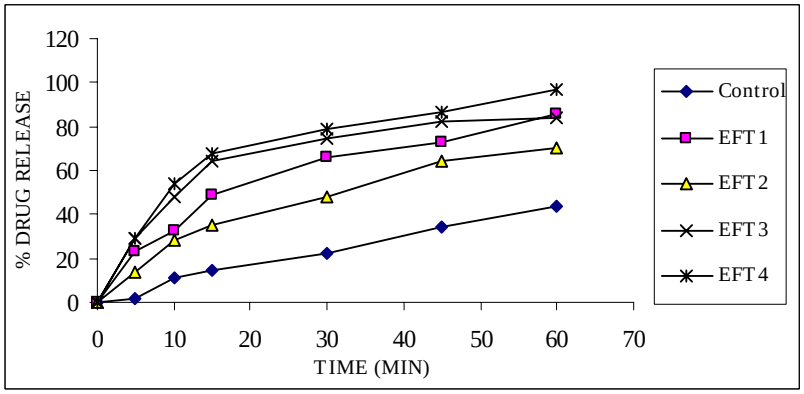
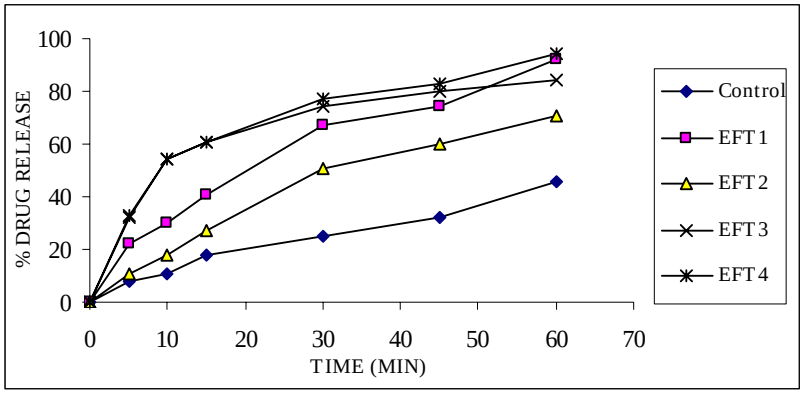
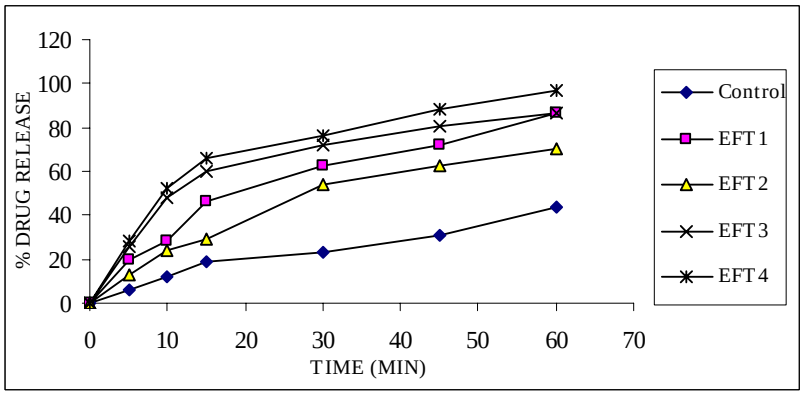


FIG NO: 6.17 COMPARATIVE DISSOLUTION PROFILE OF EFAVIRENZ 600mg AT 50 rpm IN 1000ml WATER WITH 2% SLS 60th DAY STABILITY ANALYSIS

25ºC/60%RH



30ºC-65%RH



40ºC-75%RH

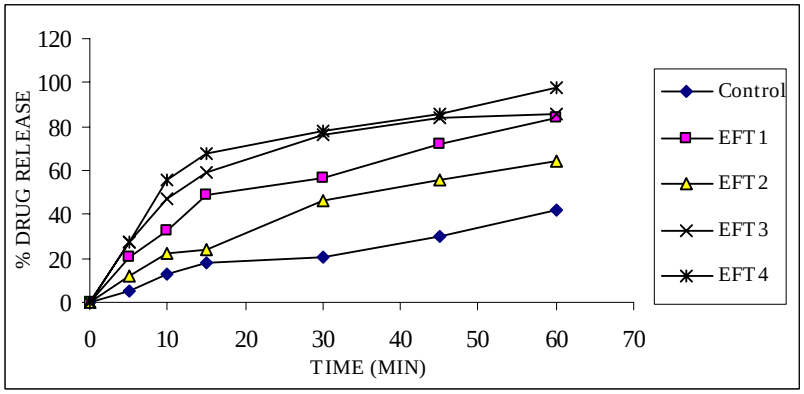


FIG NO: 6.18 COMPARATIVE DISSOLUTION PROFILE OF EFAVIRENZ 600mg AT 50 rpm IN 1000ml WATER WITH 2% SLS 90th DAY STABILITY ANALYSIS

TABLE NO: 6.22 T_{50} AND T_{80} VALUES OF EFAVIRENZ (600mg) TABLETS IN 1000 ml WITH DIFFERENT SLS CONCENTRATION

TRIALS	T_{50} IN MEDIA WITH DIFFERENT SLS CONCENTRATION		T_{80} IN MEDIA WITH DIFFERENT SLS CONCENTRATION	
	1000ml 2% SLS	1000ml 0.2% SLS	1000ml 2% SLS	1000ml 0.2% SLS
EFT_1	17.47	NA	44.27	NA
EFT_2	27.66	NA	NA	NA
EFT_3	9.16	NA	34.51	NA
EFT_4	9.62	22.21	27.54	NA

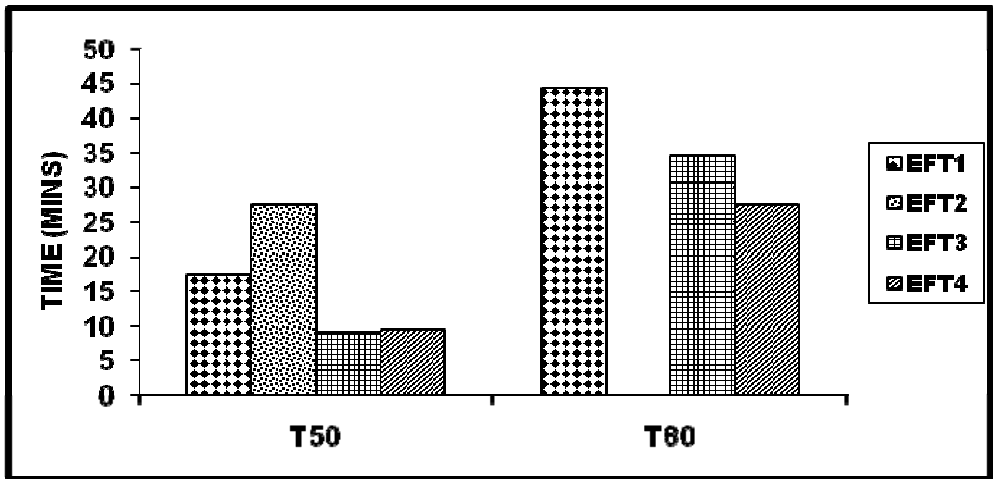


FIG NO: 6.7 COMPARISION OF T_{50} AND T_{80} VALUES OF EFAVIRENZ (600mg) TABLETS IN 1000 ml WATER WITH 2% SLS (COMPENDIA MEDIUM)

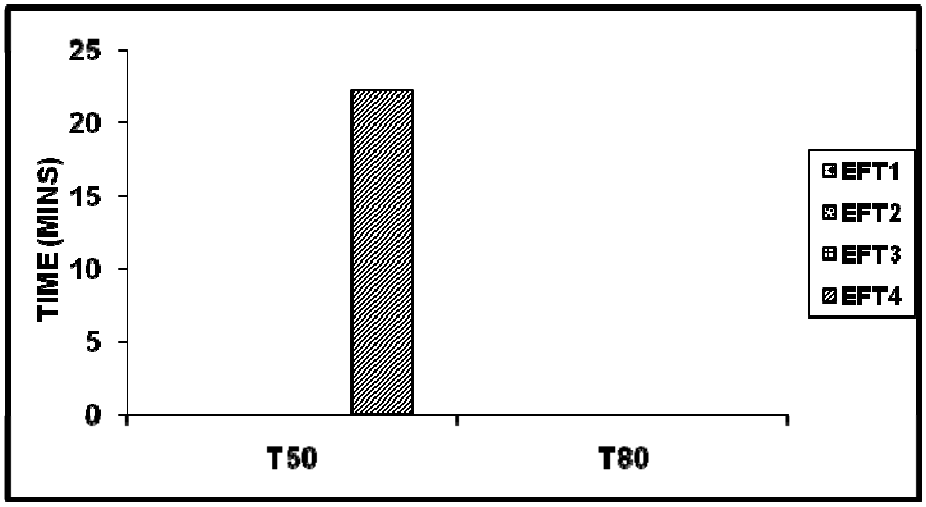
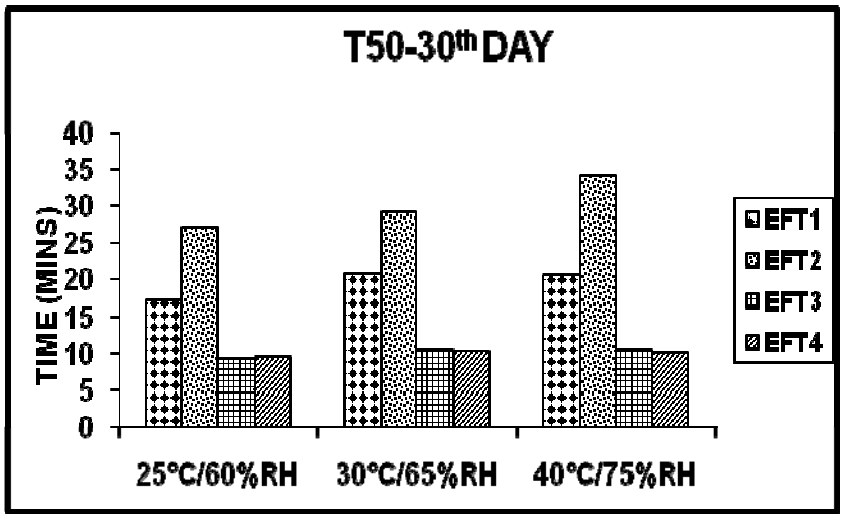


FIG NO: 6.8 T_{50} AND T_{80} VALUES OF EFAVIRENZ (600mg) TABLETS AT 50 rpm IN 1000 ml WATER WITH 0.2% SLS (QUASI SINK MEDIUM)

TABLE NO: 6.25 T_{50} AND T_{80} DATA OF EFAVIRENZ 600mg TABLETS STABILITY ANALYSIS

TRIALS	DAYS	25ºC-60%RH		30 ºC -65%RH		40 ºC -75%RH	
		T_{50}	T_{80}	T_{50}	T_{80}	T_{50}	T_{80}
EFT1	30	17.78	45.16	20.64	51.38	20.49	52.19
	60	18.91	49.94	18.28	46.29	17.47	51.32
	90	20.29	46.98	20.11	51.46	20.17	55.80
EFT2	30	27.18	NA	29.13	NA	34.01	NA
	60	26.13	NA	35.69	NA	29.00	NA
	90	48.36	NA	28.33	NA	36.85	NA
EFT3	30	9.13	32.93	10.44	36.77	10.48	40.69
	60	9.44	39.92	10.08	32.00	10.07	39.06
	90	9.39	43.68	11.17	40.16	11.07	36.75
EFT4	30	9.45	30.48	10.19	46.88	9.97	27.73
	60	8.74	40.22	8.81	29.14	9.25	26.02
	90	9.60	33.29	9.93	28.44	9.24	25.44



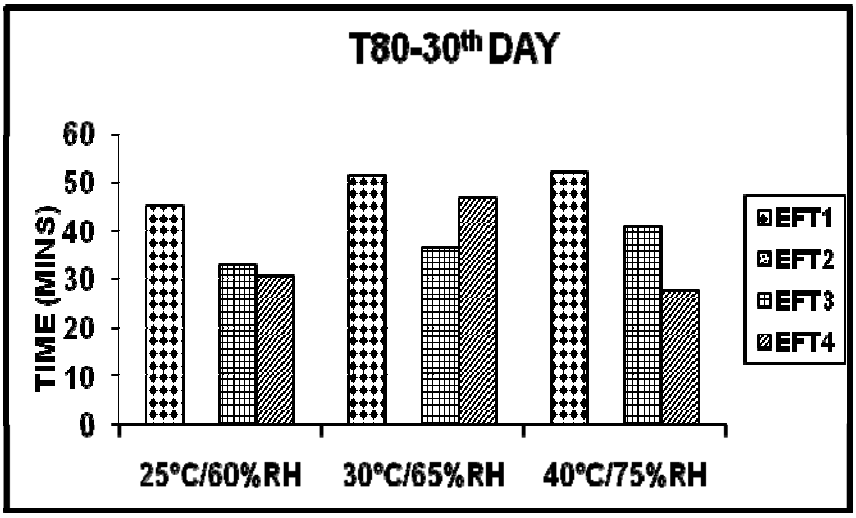
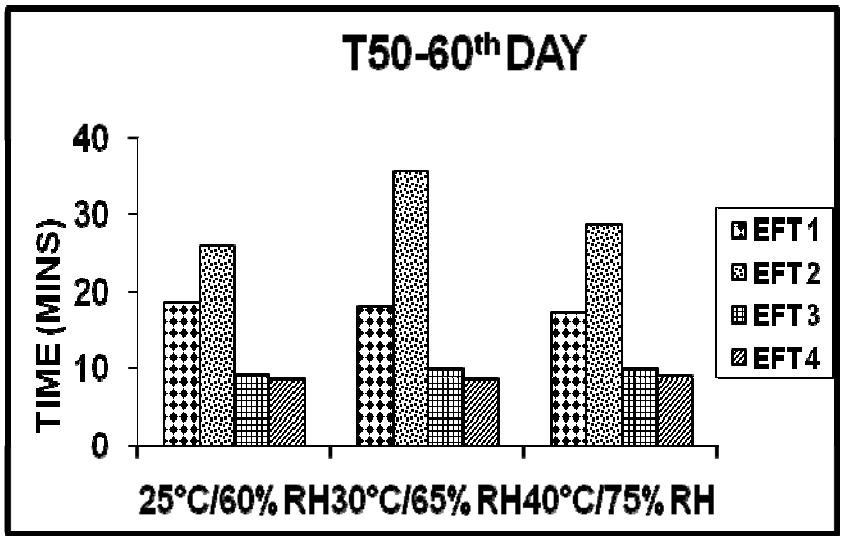


FIG NO: 6.19 T_{50} AND T_{80} DATA OF EFAVIRENZ 600mg TABLETS

30^{th} DAY STABILITY ANALYSIS



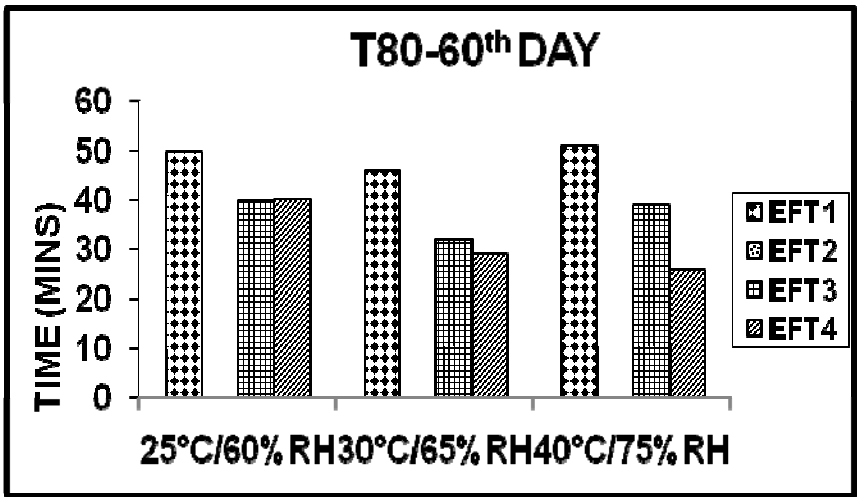
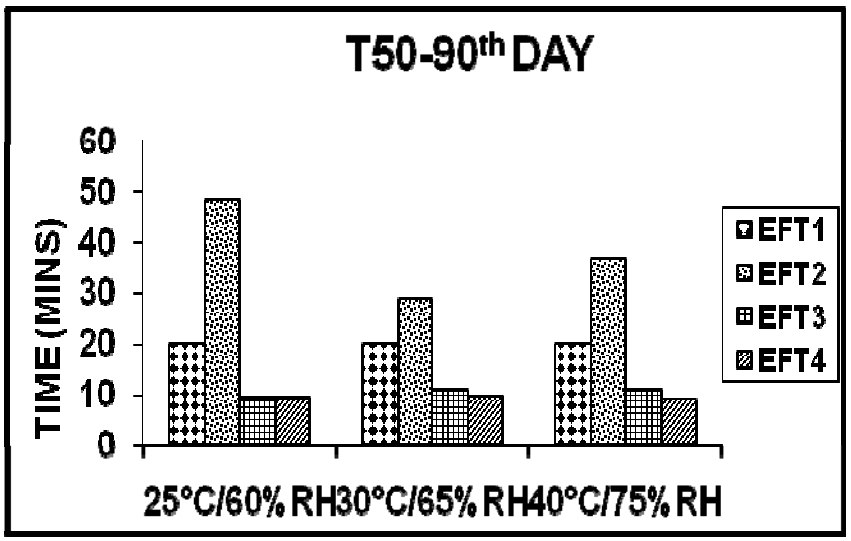


FIG NO: 6.20 T_{50} AND T_{80} DATA OF EFAVIRENZ 600mg TABLETS

60^{th} DAY STABILITY ANALYSIS



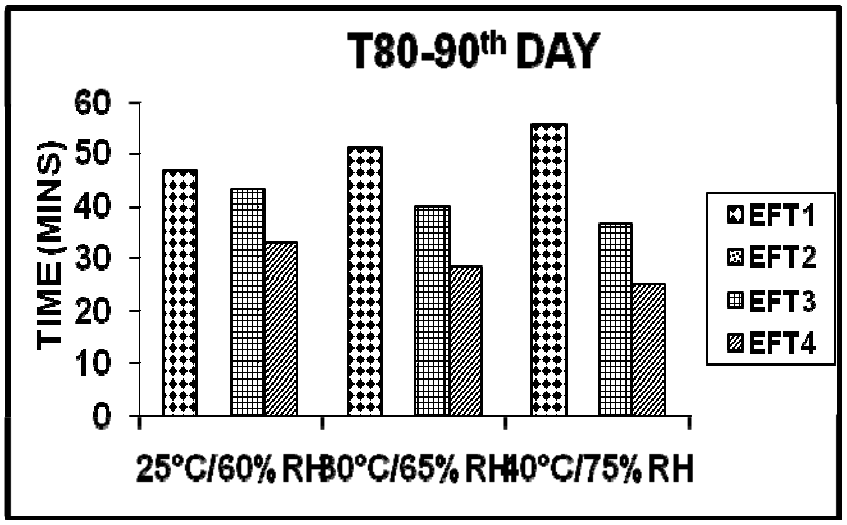


FIG NO: 6.21 T_{50} AND T_{80} DATA OF EFAVIRENZ 600mg TABLETS 90th DAY STABILITY ANALYSIS

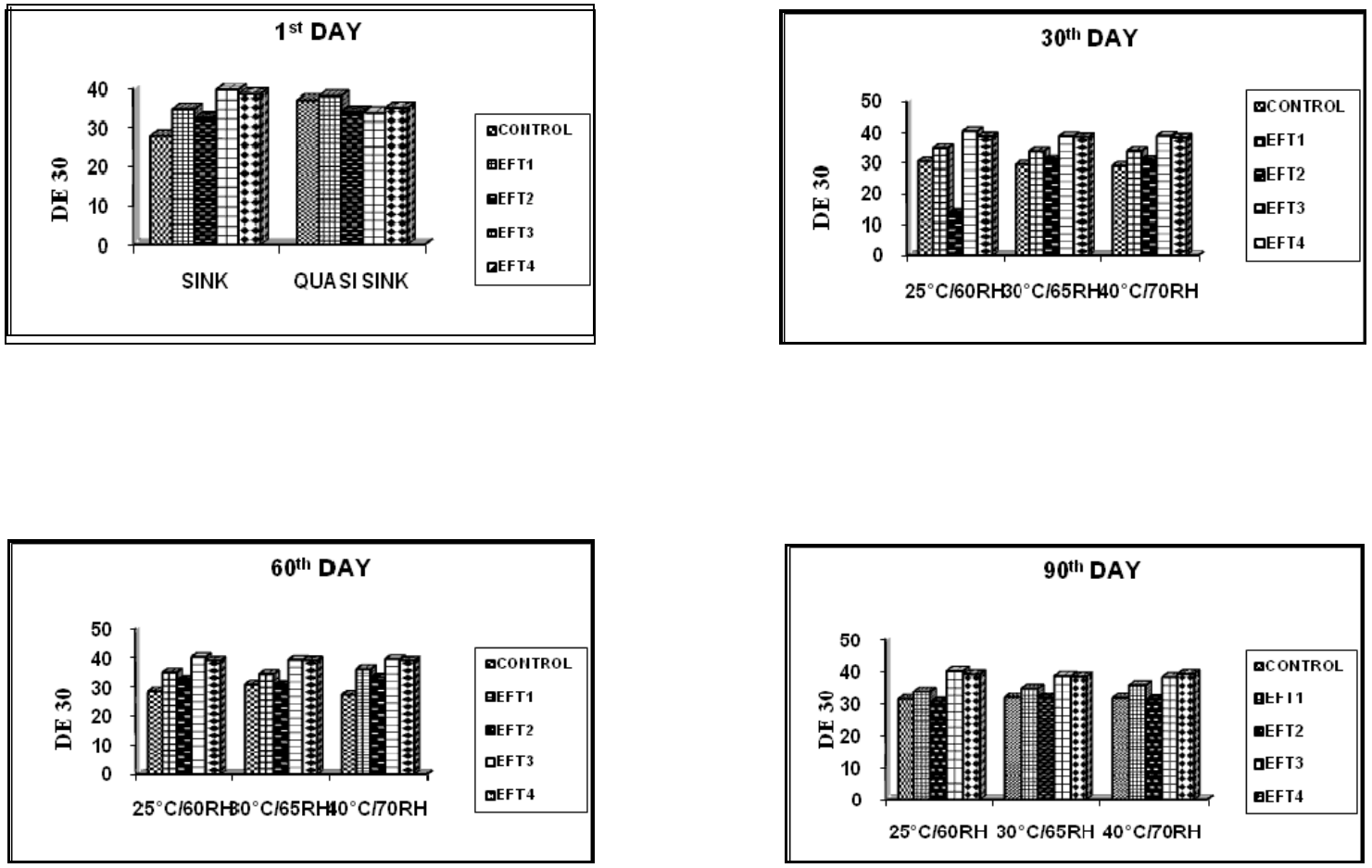


FIG NO: 6.13 Dissolution Efficiency (DE_{30}) of Efavirenz 600mg Tablets

For Acyclovir (800mg)

Table No: 6.8 Physical Parameters

Physical Parameters	Batches				
	Control	**ACT_1**	**ACT_2**	**ACT_3**	**ACT_4**
Appearance	White, capsule Shaped				
LOD for granules %L	1.64	1.53	1.68	1.72	1.96
Bulk Density (wt/ml)	0.5522	0.5448	0.5512	0.5461	0.5481
Tapped Density (wt/ml)	0.6264	0.6486	0.6312	0.6318	0.6418
% Compressibility	11.85	16.00	12.67	13.56	14.60
Assay of granules (%)	98.89	99.18	99.48	101.12	100.78

Table No: 6.9 Weight Variation (gm)

DAYS	Stability Conditions	CONTROL	ACT1	ACT2	ACT3	ACT4
1st	NA	1.5174± 0.014	1.5123± 0.009	1.5083± 0.006	1.502± 0.0051	1.5065± 0.004
30	25ºC/60%RH	1.5162± 0.02	1.5058± 0.002	1.5092± 0.001	1.5078± 0.003	1.5047± 0.003
30	30ºC/65%RH	1.5124± 0.02	1.5052± 0.004	1.5043± 0.003	1.5043± 0.003	1.5076± 0.003
30	40ºC/75%RH	1.5094± 0.3	1.5062± 0.004	1.5042± 0.0025	1.5062± 0.003	1.5031± 0.002
60	25ºC/60%RH	1.5082± 0.3	1.5104± 0.003	1.5108± 0.003	1.5106± 0.002	1.5118± 0.004
60	30ºC/65%RH	1.5034± 0.012	1.5086± 0.003	1.5104± 0.004	1.507± 0.003	1.5084± 0.002
60	40ºC/75%RH	1.5048± 0.14	1.5089± 0.003	1.506± 0.003	1.507± 0.003	1.5098± 0.002
90	25ºC/60%RH	1.5052± 0.24	1.5114± 0.004	1.5113± 0.003	1.508± 0.0024	1.5096± 0.004
90	30ºC/65%RH	1.5068± 0.3	1.5086± 0.003	1.5078± 0.002	1.5081± 0.0021	1.5073± 0.004
90	40ºC/75%RH	1.5084± 0.12	1.5071± 0.0018	1.5082± 0.0015	1.5093± 0.004	1.5093± 0.003

n=20, Mean ± S.D

Table No: 6.10 Hardness (N)

DAYS	Stability Conditions	CONTROL	ACT1	ACT2	ACT3	ACT4
1st	NA	153±0.3	160±0.3	147±0.2	118±0.5	141±0.5
30	25ºC/60%RH	161±0.2	145±0.3	141±0.2	113±0.4	139±0.2
30	30ºC/65%RH	154±0.3	142±0.2	139±0.2	117±0.2	139±0.2
30	40ºC/75%RH	168±0.3	142±0.4	139±0.2	105±0.3	137±0.4
60	25ºC/60%RH	158±0.2	150±0.5	144±0.3	126±0.3	136±0.8
60	30ºC/65%RH	155±0.3	150±0.6	149±0.7	128±0.2	146±0.2
60	40ºC/75%RH	156±0.3	157±0.5	149±0.2	125±0.5	137±0.5
90	25ºC/60%RH	161±0.2	150±0.4	151±0.3	131±0.4	138±0.9
90	30ºC/65%RH	162±0.3	152±0.4	153±0.4	130±0.2	148±0.2
90	40ºC/75%RH	154±0.3	150±0.3	142±0.4	129±0.2	133±0.8

n=10, Mean ± S.D.

Table No: 6.11 Friability (%)

DAYS	Stability Conditions	CONTROL	ACT1	ACT2	ACT3	ACT4
1st	NA	0.118	0.054	0.119	0.276	0.046
30	25ºC/60%RH	0.054	0.14	0.13	0.075	0.035
30	30ºC/65%RH	0.256	0.197	0.133	0.055	0.132
30	40ºC/75%RH	0.356	0.134	0.009	0.137	0.018
60	25ºC/60%RH	0.127	0.086	0.09	0.074	0.018
60	30ºC/65%RH	0.258	0.018	0.24	0.075	0.032
60	40ºC/75%RH	0.123	0.083	0.081	0.172	0.091
90	25ºC/60%RH	0.123	0.078	0.039	0.124	0.076
90	30ºC/65%RH	0.152	0.012	0.072	0.064	0.077
90	40ºC/75%RH	0.165	0.14	0.09	0.179	0.147

Table No: 6.12 Disintegration Time (min)

DAYS	Stability Conditions	CONTROL	ACT1	ACT2	ACT3	ACT4
1st	NA	10.06±0.4	6.15±0.7	9.54±0.8	3.28±0.6	5.24±1.1
30	25ºC/60%RH	11.06±0.3	9.07±0.2	7.43±0.4	2.5±0.4	5.11±0.2
30	30ºC/65%RH	12.05±0.1	6.53±0.2	5.4±0.2	2.44±0.3	3.44±0.1
30	40ºC/75%RH	11.56±0.1	9.16±0.2	8.18±0.3	2.24±0.2	3.47±0.2
60	25ºC/60%RH	12.10±0.1	10.46±0.3	9.17±0.2	3.18±0.4	5.38±0.2
60	30ºC/65%RH	11.52±0.2	7.23±0.1	7.35±0.3	3.26±0.5	4.28±0.1
60	40ºC/75%RH	11.46±0.3	9.24±0.2	8.12±0.2	3.31±0.3	4.35±0.2
90	25ºC/60%RH	10.56±0.4	10.53±0.2	10.30±0.2	3.39±0.3	6.14±0.2
90	30ºC/65%RH	10.54±0.3	7.21±0.3	8.18±0.3	3.25±0.2	4.05±0.1
90	40ºC/75%RH	10.52±0.1	9.28±0.1	8.52±0.1	3.47±0.3	5.30±0.1

n=6, Mean ± S.

Table No: 6.13 LOD for Tablets %L

DAYS	Stability Conditions	CONTROL	ACT1	ACT2	ACT3	ACT4
1st	NA	1.59	1.82	1.66	1.99	1.95
30	25ºC/60%RH	1.98	1.98	1.98	1.98	2.12
30	30ºC/65%RH	1.97	2.13	1.96	2.15	2.13
30	40ºC/75%RH	1.85	2.46	1.93	2.36	2.15
60	25ºC/60%RH	1.59	2.15	2.05	2.45	2.27
60	30ºC/65%RH	1.65	2.16	2.15	2.14	2.29
60	40ºC/75%RH	1.97	2.33	2.31	2.33	2.14
90	25ºC/60%RH	1.65	2.15	2.25	2.12	2.31
90	30ºC/65%RH	1.96	2.45	2.24	2.18	2.12
90	40ºC/75%RH	1.78	2.44	1.98	1.95	2.04

Table No: 6.14 Assay for Tablets (%)

DAYS	Stability Conditions	CONTROL	ACT1	ACT2	ACT3	ACT4
1st	NA	98.45	99.55	99.46	100.31	100.31
30	25ºC/60%RH	98.21	101.02	102.78	102.12	99.14
30	30ºC/65%RH	97.54	99.09	99.14	101.04	98.14
30	40ºC/75%RH	99.12	99.72	99.17	99.78	100.12
60	25ºC/60%RH	101.12	101.62	101.14	101.26	100.78
60	30ºC/65%RH	99.52	99.78	98.98	99.47	99.37
60	40ºC/75%RH	98.25	99.98	98.17	99.12	98.96
90	25ºC/60%RH	98.32	101.78	101.34	101.34	100.34
90	30ºC/65%RH	97.35	99.24	99.64	99.64	98.93
90	40ºC/75%RH	97.25	99.12	98.97	98.97	99.17

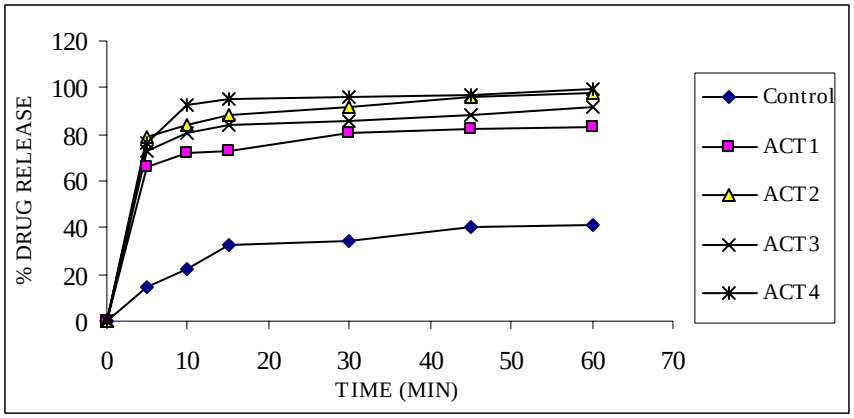


FIG NO: 6.3 COMPARATIVE DISSOLUTION PROFILE OF ACYCLOVIR 800mg IN 900ml 0.1N HCl (COMPENDIA MEDIUM) ON 1st DAY

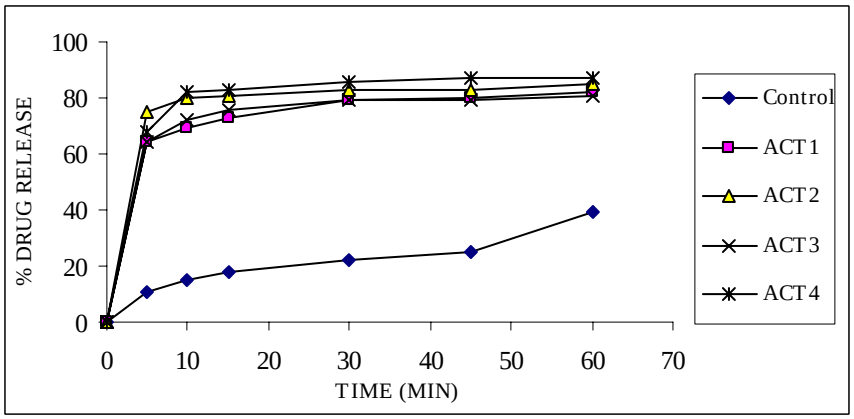
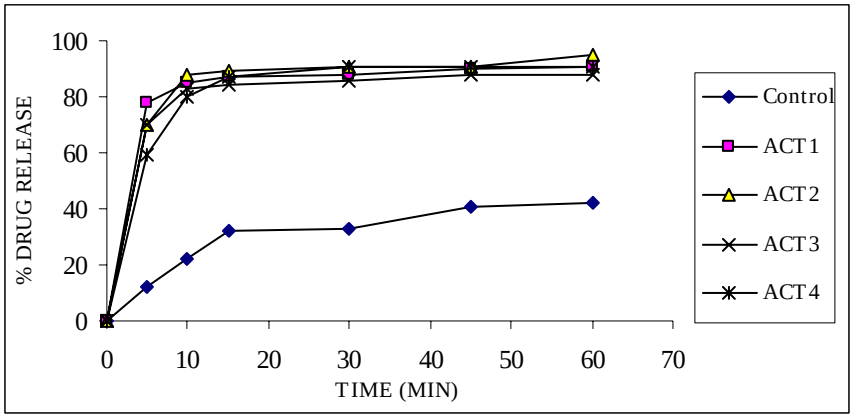
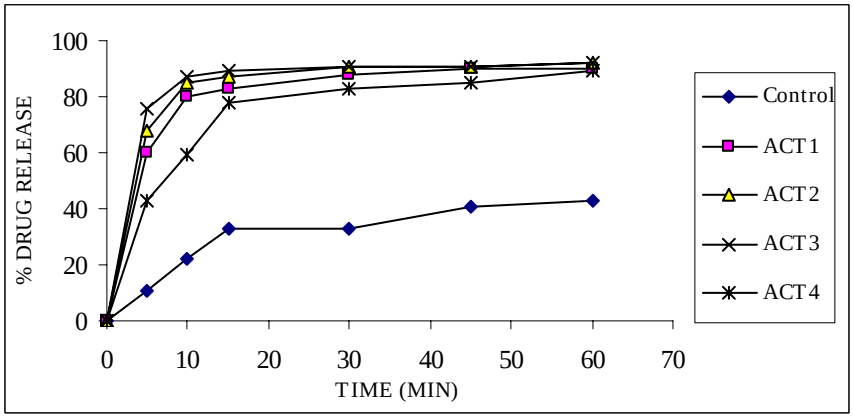


FIG NO: 6.4 COMPARATIVE DISSOLUTION PROFILE OF ACYCLOVIR 800mg IN 500 ml 0.1N HCl (QUASI SINK) ON 1st DAY

25ºC/60%RH



30ºC-65%RH



40ºC-75%RH

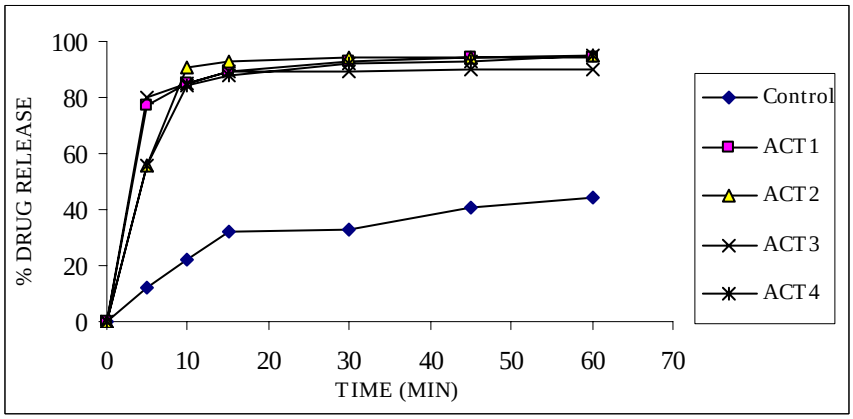
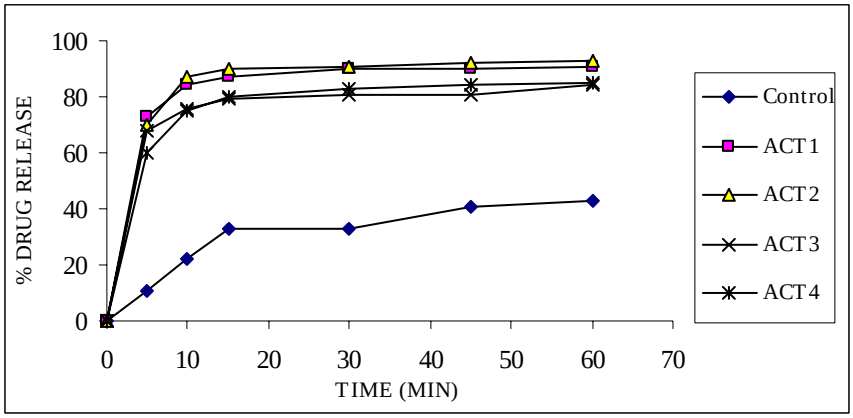
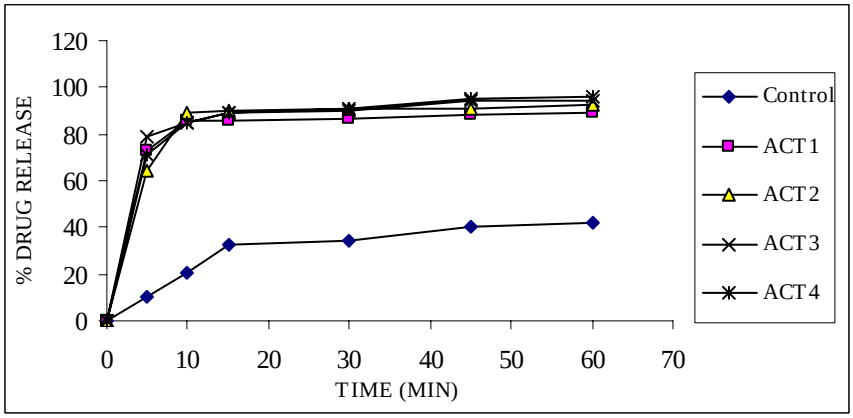


FIG NO: 6.22 COMPARATIVE DISSOLUTION PROFILE OF ACYCLOVIR 800mg IN 900 ml 0.1N HCl 30th DAY STABILITY ANALYSIS

25ºC/60%RH



30ºC-65%RH



40ºC-75%RH

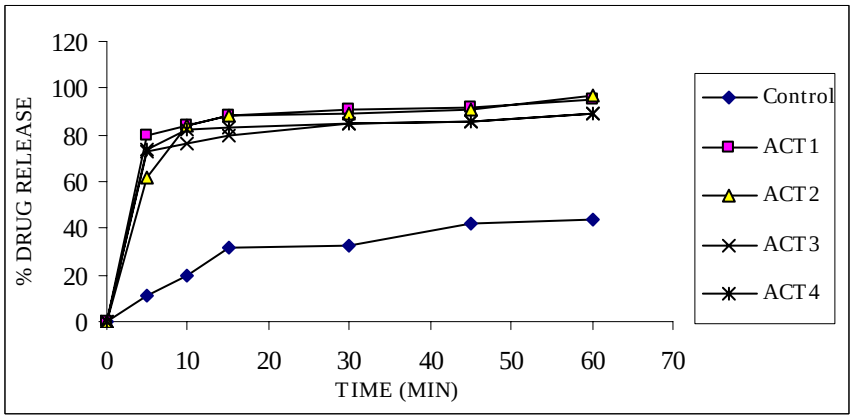
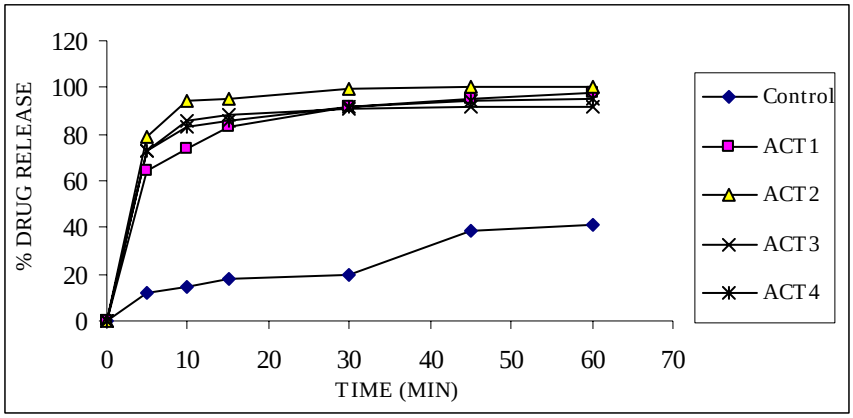
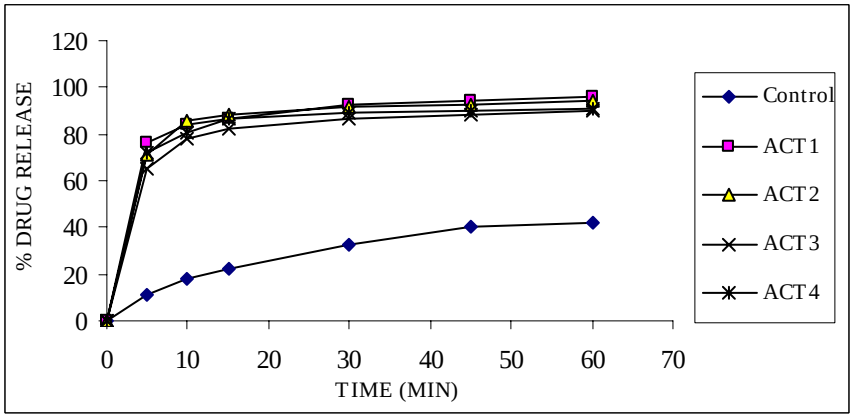


FIG NO: 6.23 COMPARATIVE DISSOLUTION PROFILE OF ACYCLOVIR 800mg IN 900 ml 0.1N HCl 60th DAY STABILITY ANALYSIS

25ºC/60%RH



30ºC-65%RH



40ºC-75%RH

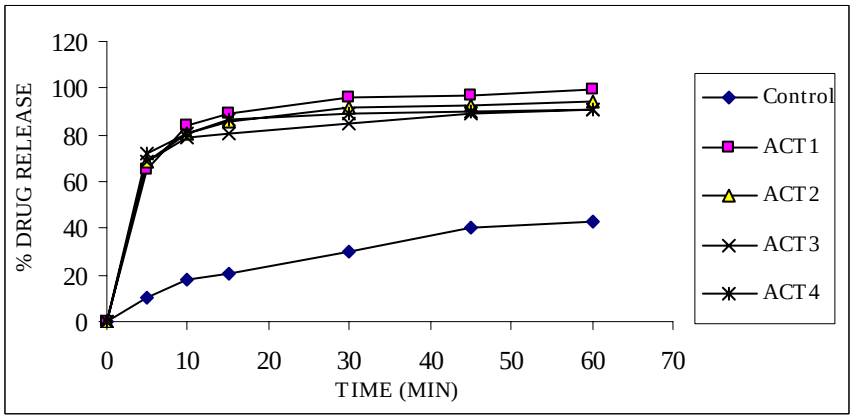


FIG NO: 6.24 COMPARATIVE DISSOLUTION PROFILE OF ACYCLOVIR 800mg IN 900 ml 0.1N HCl 90th DAY STABILITY ANALYSIS

TABLE NO: 6.23 T_{50} AND T_{80} VALUES OF ACYCLOVIR (800mg) TABLETS AT 50 rpm WITH 0.1N HCl

TRIALS	T_{50} IN 0.1N HCl		T_{80} IN 0.1N HCl	
	900ml (COMPENDIA)	500ml (QUASI SINK)	900ml (COMPENDIA)	500ml (QUASI SINK)
ACT_1	0.87	1.23	32.81	41.51
ACT_2	0.08	0.77	5.70	11.08
ACT_3	0.93	2.36	9.74	47.13
ACT_4	2.99	3.01	5.56	9.08

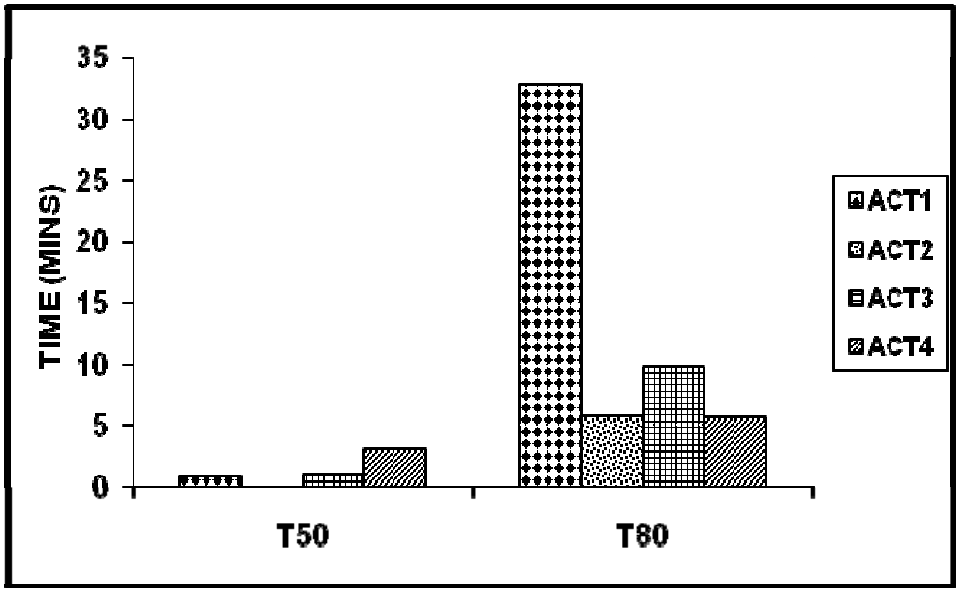


FIG NO: 6.9 COMPARATIVE T_{50} AND T_{80} DATA OF ACYCLOVIR 800mg TABLETS AT 50 rpm IN 900 ml 0.1N HCl (COMPENDIA MEDIUM)

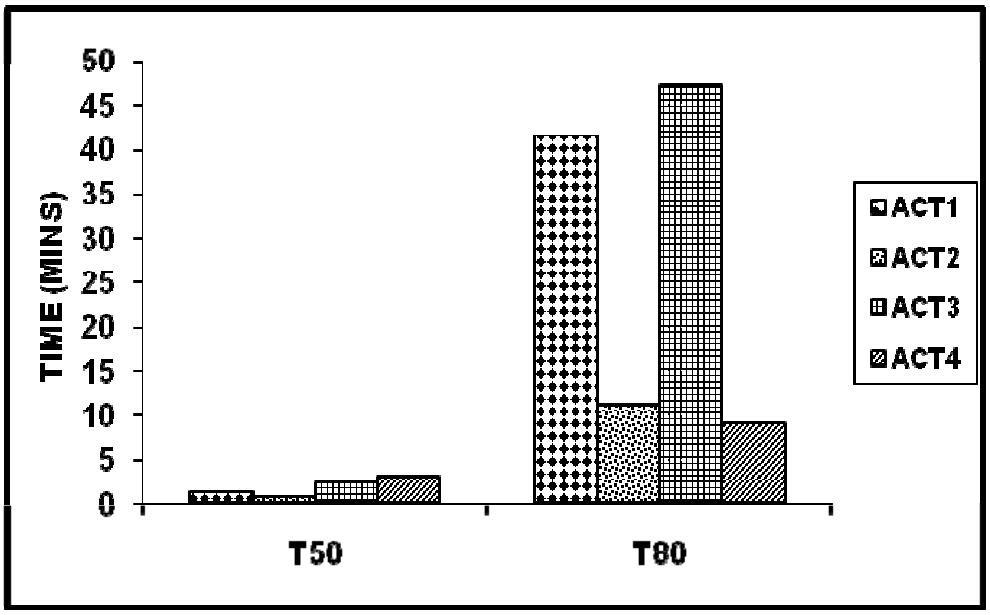
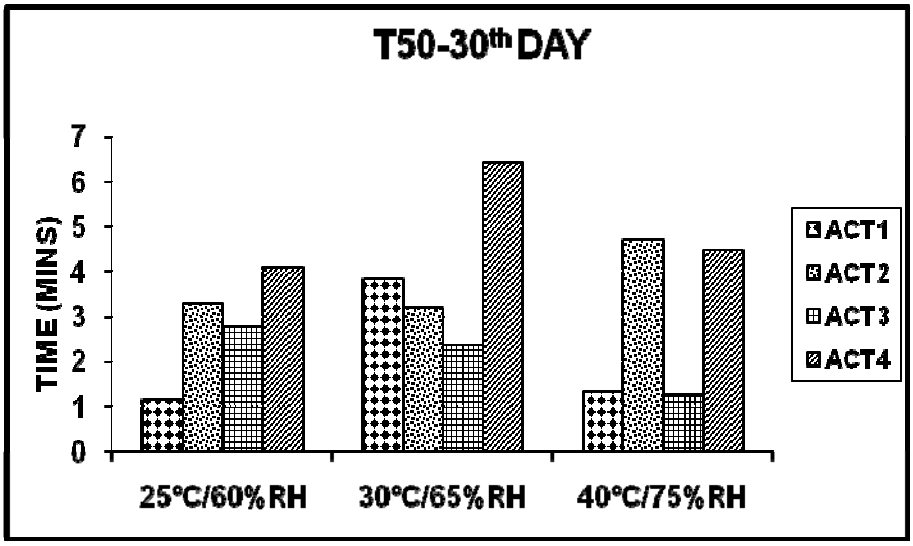


FIG NO: 6.10 COMPARATIVE T_{50} AND T_{80} DATA OF ACYCLOVIR 800mg TABLET AT 50 rpm IN 500 ml 0.1N HCl (QUASI SINK MEDIUM)

TABLE NO: 6.26 T_{50} AND T_{80} DATA OF ACYCLOVIR 800mg TABLETS

STABILITY ANALYSIS

TRIALS	DAYS	25ºC-60%RH		30ºC -65%RH		40ºC -75%RH	
		T_{50}	T_{80}	T_{50}	T_{80}	T_{50}	T_{80}
ACT1	30	1.14	5.88	3.82	10.72	1.34	6.21
	60	2.27	7.31	3.11	6.49	0.14	5.04
	90	2.42	13.12	3.43	15.76	3.21	8.58
ACT2	30	3.29	6.79	3.19	7.77	4.70	6.89
	60	3.29	6.83	4.19	6.70	3.79	8.69
	90	2.35	5.15	2.66	7.30	2.29	9.21
ACT3	30	2.77	8.34	2.35	6.02	1.26	5.05
	60	1.96	19.81	0.63	5.49	0.11	15.80
	90	2.52	6.85	2.73	12.10	1.29	12.95
ACT4	30	4.09	9.73	6.42	22.26	4.47	8.88
	60	3.65	15.56	2.37	7.61	1.23	8.90
	90	1.42	8.15	2.02	8.38	2.02	8.38



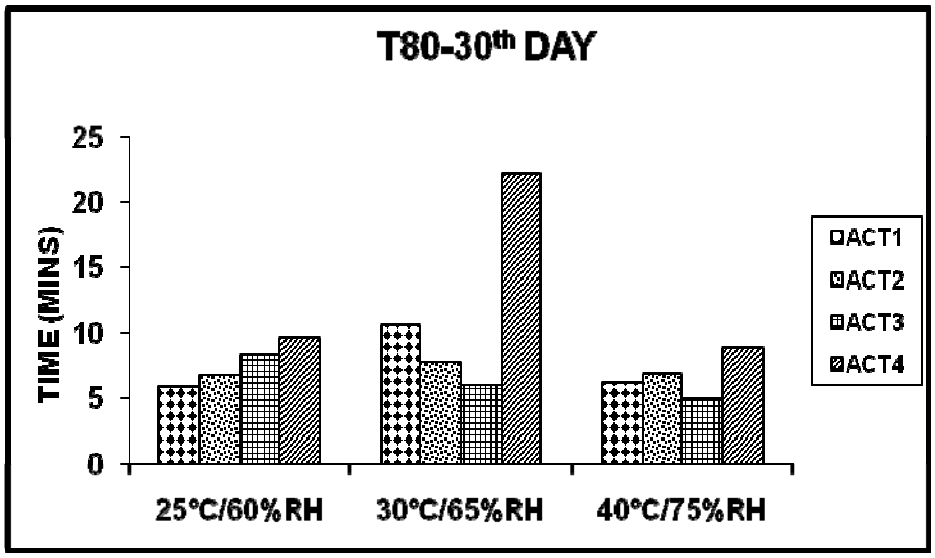
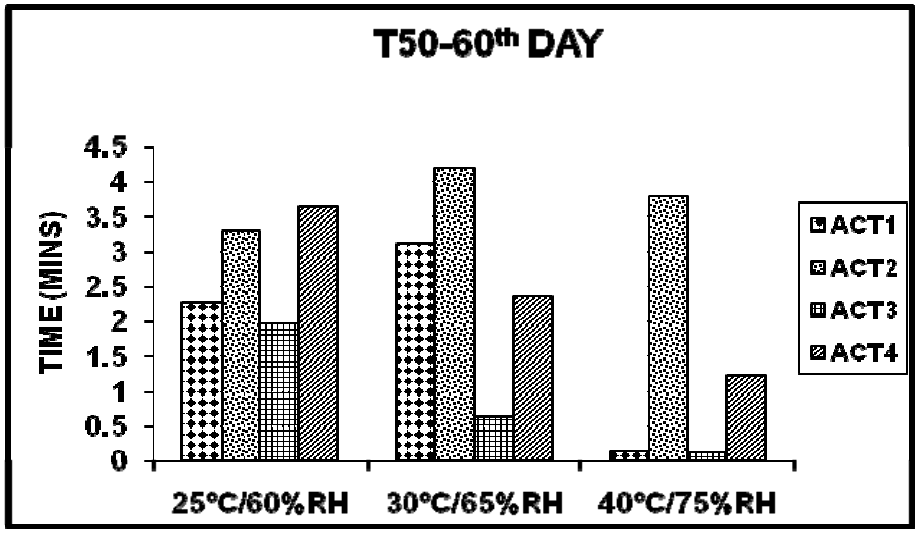


FIG NO: 6.25 COMPARATIVE T_{50} AND T_{80} DATA OF ACYCLOVIR 800mg 30th DAY STABILITY ANALYSIS



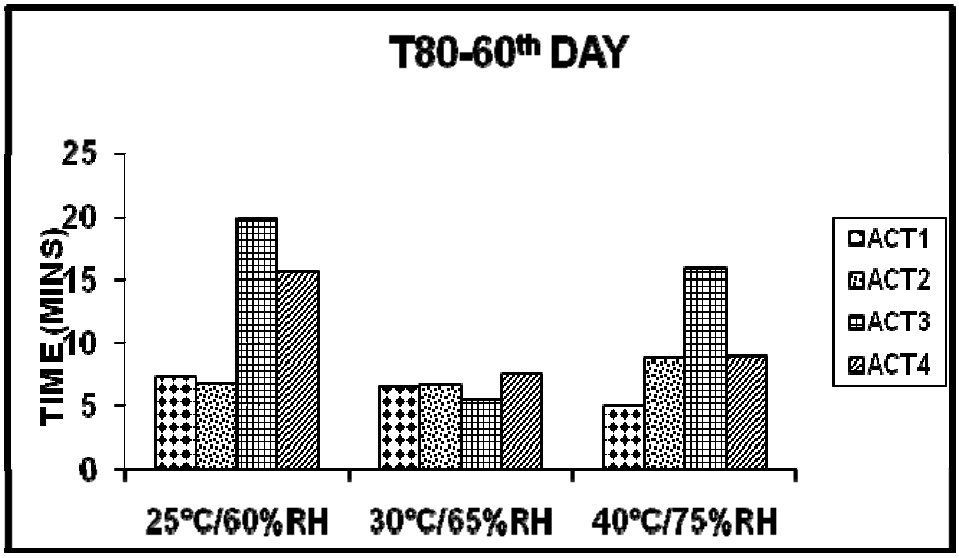
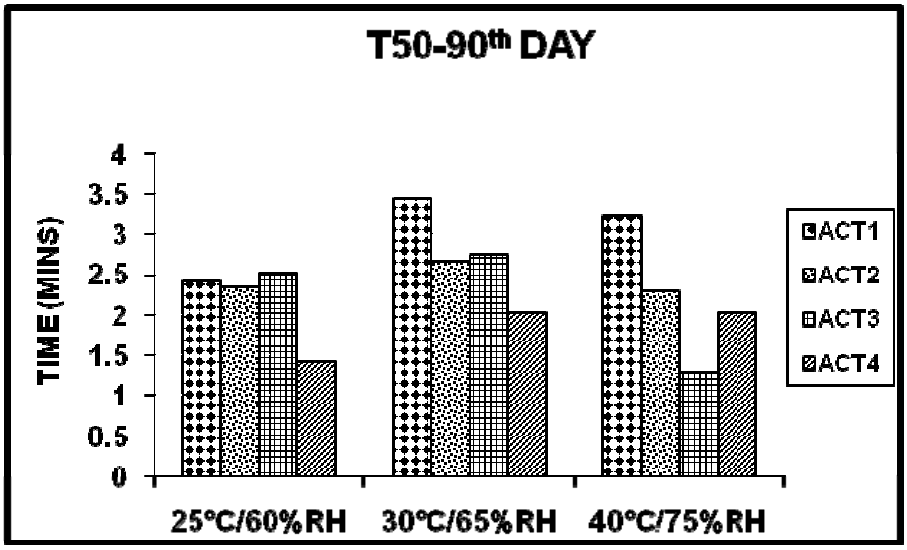


FIG NO: 6.26 COMPARATIVE T_{50} AND T_{80} DATA OF ACYCLOVIR 800mg 60th DAY STABILITY ANALYSIS



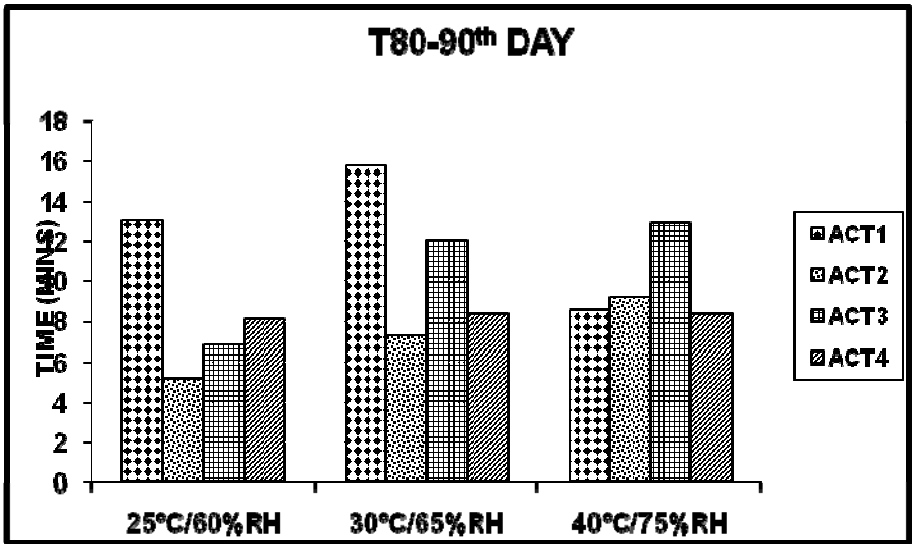


FIG NO: 6.27 COMPARATIVE T_{50} AND T_{80} DATA OF ACYCLOVIR 800mg 90th DAY STABILITY ANALYSIS

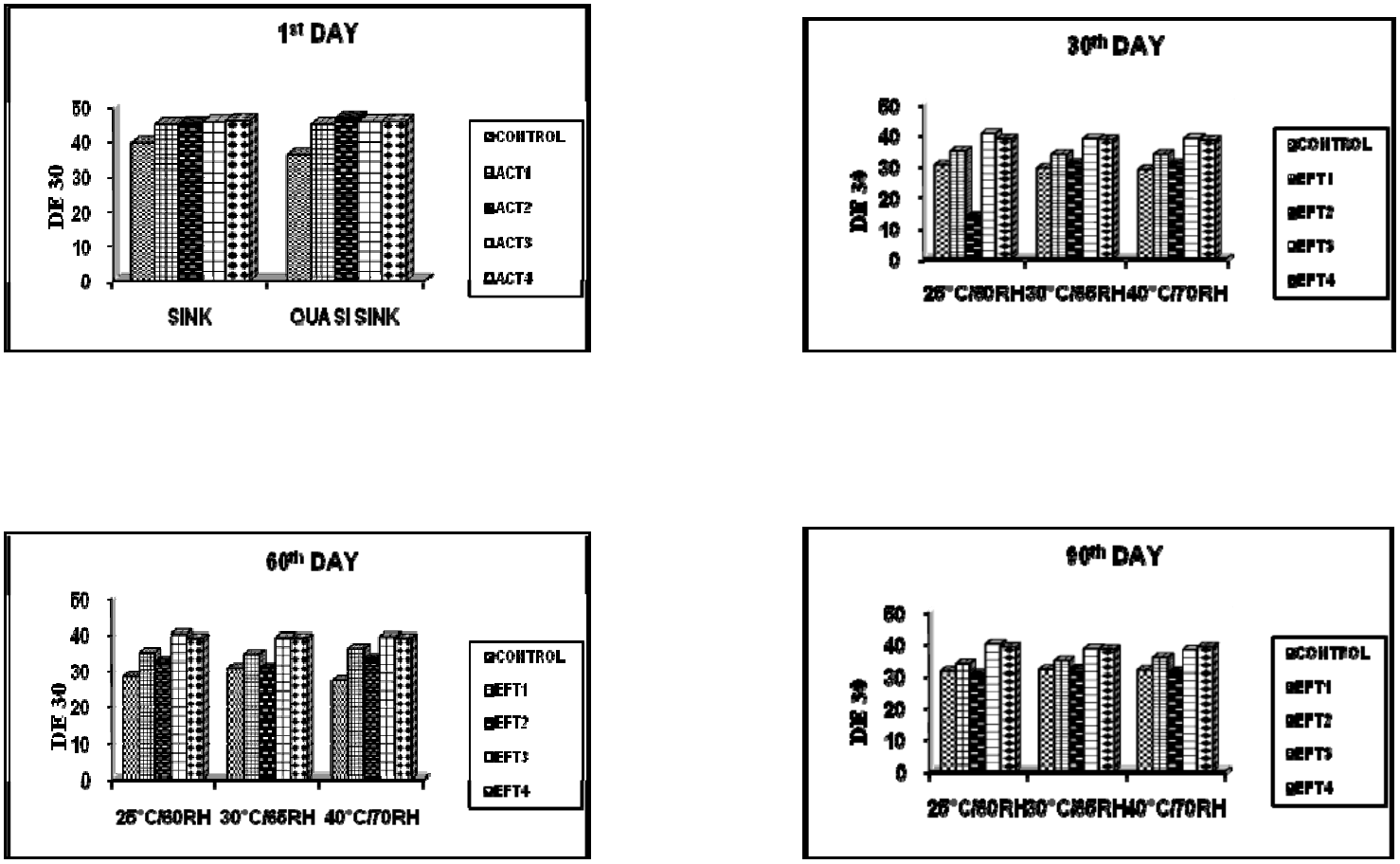


FIG NO: 6.14 Dissolution Efficiency (DE_{30}) of Acyclovir 800mg Tablets

For Nevirapine (200mg)

Table No: 6.15 Physical Parameters

Physical Parameters	Batches				
	Control	NET_1	NET_2	NET_3	NET_4
Appearance	White, capsule Shaped				
LOD for granules %L	1.64	1.68	1.72	1.86	1.89
Bulk Density (wt/ml)	0.4542	0.432	0.418	0.436	0.438
Tapped Density (wt/ml)	0.5164	0.5273	0.5185	0.5215	0.5286
% Compressibility	12.04	18.07	19.38	16.4	17.14
Assay of granules (%)	98.89	99.8	100.8	100.6	101.8

Table No: 6.16 Weight Variation (gm)

DAYS	Stability Conditions	CONTROL	NET1	NET2	NET3	NET4
1st	NA	0.854± 0.024	0.852± 0.001	0.852± 0.0014	0.853± 0.0016	0.854± 0.0026
30	25ºC/60%RH	0.8532± 0.02	0.8530 ± 0.002	0.8532 ± 0.001	0.8525 ± 0.002	0.8527 ± 0.01
30	30ºC/65%RH	0.8584± 0.02	0.8524 ± 0.002	0.8515 ± 0.001	0.8520 ± 0.002	0.8527 ± 0.0007
30	40ºC/75%RH	0.8592± 0.001	0.8522 ± 0.002	0.8534 ± 0.002	0.8527 ± 0.0009	0.8521 ± 0.001
60	25ºC/60%RH	0.8564± 0.02	0.8532 ± 0.002	0.8544 ± 0.002	0.8534 ± 0.002	0.854± 0.002
60	30ºC/65%RH	0.8532± 0.01	0.8535 ± 0.002	0.8541 ± 0.002	0.8526 ± 0.002	0.8502 ± 0.002
60	40ºC/75%RH	0.8564± 0.002	0.8534 ± 0.003	0.8527 ± 0.002	0.8525 ± 0.0012	0.853± 0.002
90	25ºC/60%RH	0.8512± 0.001	0.8542 ± 0.002	0.8544 ± 0.002	0.8541 ± 0.002	0.8543 ± 0.002
90	30ºC/65%RH	0.8524± 0.01	0.854± 0.002	0.8534 ± 0.002	0.8533 ± 0.002	0.8537 ± 0.0012
90	40ºC/75%RH	0.8562± 0.02	0.8531 ± 0.002	0.8527 ± 0.001	0.8525 ± 0.002	0.8530 ± 0.0016

n=20, Mean ± S.D

Table No: 6.17 Hardness (N)

DAYS	Stability Conditions	CONTROL	NET1	NET2	NET3	NET4
1st	NA	103±0.35	103.4± 0.346	104.2± 0.245	106.4± 0.562	103.6± 0.456
30	25ºC/60%RH	105±0.02	96± 0.374	104± 0.374	96± 0.374	108± 0.51
30	30ºC/65%RH	108±0.012	102± 0.25	90± 0.32	93± 0.51	97± 0.25
30	40ºC/75%RH	110±0.03	102± 0.24	98± 0.25	94± 0.37	97± 0.35
60	25ºC/60%RH	114±0.02	103± 0.258	107± 0.5	104± 0.65	110± 0.56
60	30ºC/65%RH	115±0.01	108± 0.28	98± 0.48	98± 0.51	113± 0.19
60	40ºC/75%RH	116±0.02	111± 0.37	101± 0.4	103± 0.54	108± 0.4
90	25ºC/60%RH	108±0.01	111± 0.47	106± 0.64	108± 0.47	110± 0.48
90	30ºC/65%RH	110±0.03	112± 0.43	105± 0.61	103± 0.8	110± 0.39
90	40ºC/75%RH	108±0.02	111± 0.58	107.2± 0.19	104± 0.55	111± 0.47

n=10, Mean ± S.D

Table No: 6.18 Friability (%)

DAYS	Stability Conditions	CONTROL	NET1	NET2	NET3	NET4
1st	NA	0.018	0.023	0.105	0.099	0.098
30	25ºC/60%RH	0.018	0.049	0.004	0.046	0.026
30	30ºC/65%RH	0.156	0.054	0.042	0.113	0.087
30	40ºC/75%RH	0.025	0.09	0.016	0.131	0.094
60	25ºC/60%RH	0.065	0.04	0.016	0.136	0.112
60	30ºC/65%RH	0.098	0.133	0.117	0.068	0.103
60	40ºC/75%RH	0.152	0.148	0.12	0.105	0.021
90	25ºC/60%RH	0.012	0.098	0.213	0.225	0.17
90	30ºC/65%RH	0.132	0.061	0.193	0.035	0.131
90	40ºC/75%RH	0.015	0.115	0.024	0.134	0.134

Table No: 6.19 Disintegration Time (min)

DAYS	Stability Conditions	CONTROL	NET1	NET2	NET3	NET4
1st	NA	3.06±0.4	2.0±0.06	0.46±0.08	0.10±0.05	0.09±0.01
30	25ºC/60%RH	4.10±0.1	1.01±0.1	0.45±0.2	0.10±0.1	0.09±0.2
30	30ºC/65%RH	4.12±0.25	0.58±0.2	1.03±0.1	0.09±0.2	0.13±0.1
30	40ºC/75%RH	3.55±0.26	1.07±0.1	0.57±0.2	0.09±0.1	0.09±0.2
60	25ºC/60%RH	4.01±0.36	1.28±0.1	0.49±0.2	0.12±0.2	0.09±0.1
60	30ºC/65%RH	3.18±0.12	1.18±0.1	1.05±0.3	0.11±0.1	0.14±0.2
60	40ºC/75%RH	3.25±0.2	1.18±0.1	1.04±0.1	0.10±0.2	0.09±0.1
90	25ºC/60%RH	3.48±0.21	1.17±0.2	0.49±0.3	0.11±0.2	0.12±0.2
90	30ºC/65%RH	3.52±0.32	1.07±0.4	1.09±0.4	0.10±0.1	0.14±0.1
90	40ºC/75%RH	3.42±0.12	1.13±0.1	0.59±0.1	0.10±0.2	0.10±0.2

n=6, Mean ± S.D

Table No: 6.20 LOD for Tablets %L

DAYS	Stability Conditions	CONTROL	NET1	NET2	NET3	NET4
1st	NA	1.97	1.98	1.78	1.98	1.99
30	25ºC/60%RH	1.96	1.69	1.89	2.15	2.11
30	30ºC/65%RH	2.15	1.65	2.15	1.93	1.69
30	40ºC/75%RH	2.16	2.11	2.16	2.15	1.65
60	25ºC/60%RH	2.11	2.15	2.15	1.69	2.13
60	30ºC/65%RH	2.08	1.96	1.97	1.68	1.96
60	40ºC/75%RH	1.96	2.15	2.10	1.88	1.86
90	25ºC/60%RH	1.69	1.65	2.10	2.14	2.13
90	30ºC/65%RH	1.65	1.98	1.87	2.15	1.96
90	40ºC/75%RH	1.98	1.99	2.20	2.46	1.98

Table No: 6.21 Assay for Tablets (%)

DAYS	Stability Conditions	CONTROL	NET1	NET2	NET3	NET4
1st	NA	98.4	99.4	99.8	98.9	101.3
30	25ºC/60%RH	99.45	98.17	99.14	100.12	99.12
30	30ºC/65%RH	99.87	99.14	98.78	99.86	99.14
30	40ºC/75%RH	98.15	99.12	99.19	99.76	99.78
60	25ºC/60%RH	96.56	98.12	99.12	100.13	100.26
60	30ºC/65%RH	97.89	99.14	99.78	99.14	99.34
60	40ºC/75%RH	98.63	98.12	98.16	99.26	99.56
90	25ºC/60%RH	96.32	100.12	99.74	100.76	101.10
90	30ºC/65%RH	98.65	99.78	99.17	100.12	102.12
90	40ºC/75%RH	97.56	99.14	98.94	100.14	101.08

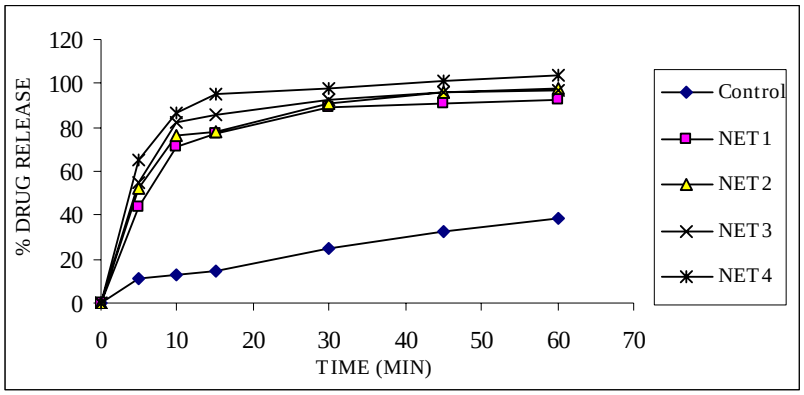


FIG NO: 6.5 COMPARATIVE DISSOLUTION PROFILE OF NEVIRAPINE 200mg AT 50 rpm IN 900 ml 0.1M pH 2 PHOSPHATE BUFFER (COMPENDIA MEDIUM) ON 1st DAY

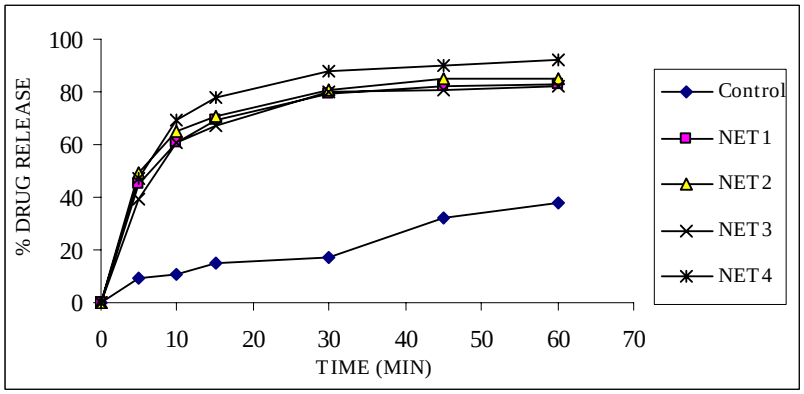
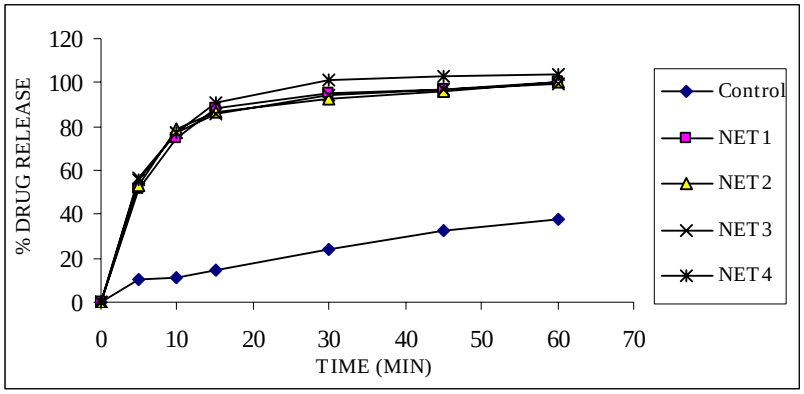
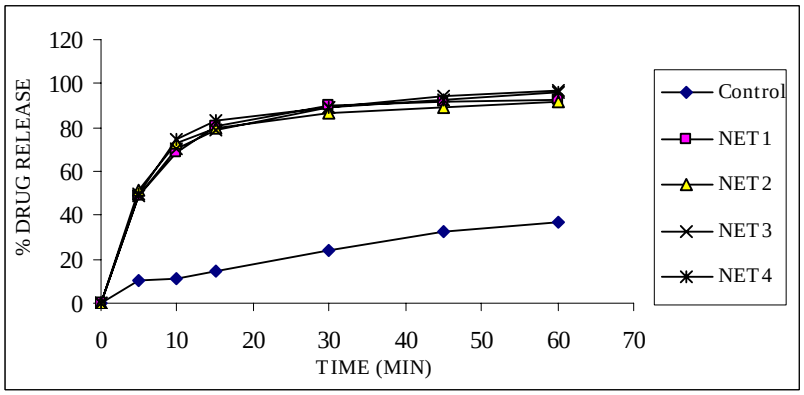


FIG NO: 6.6 COMPARATIVE DISSOLUTION PROFILE OF NEVIRAPINE 200mg AT 50 rpm IN 500 ml 0.1M pH 2 PHOSPHATE BUFFER (QUASI SINK MEDIUM) ON 1st DAY

25ºC/60%RH



30ºC-65%RH



40ºC-75%RH

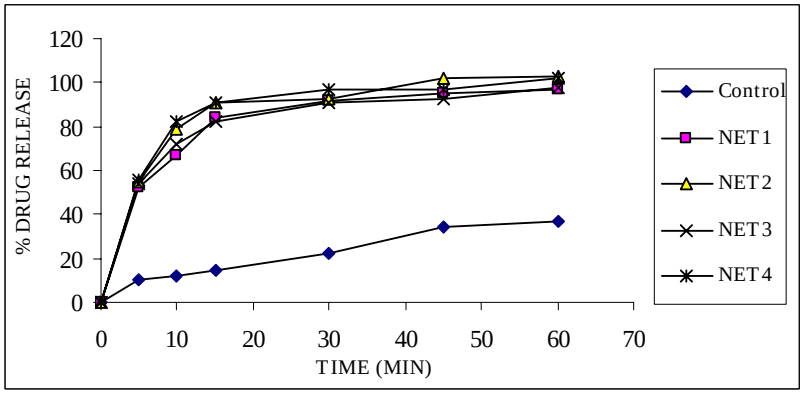
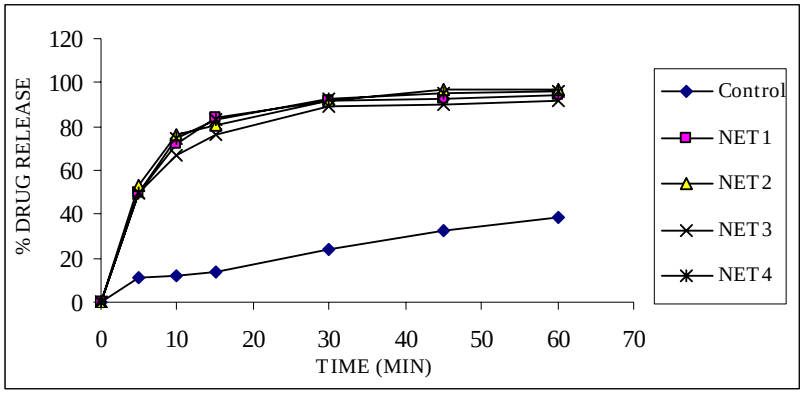
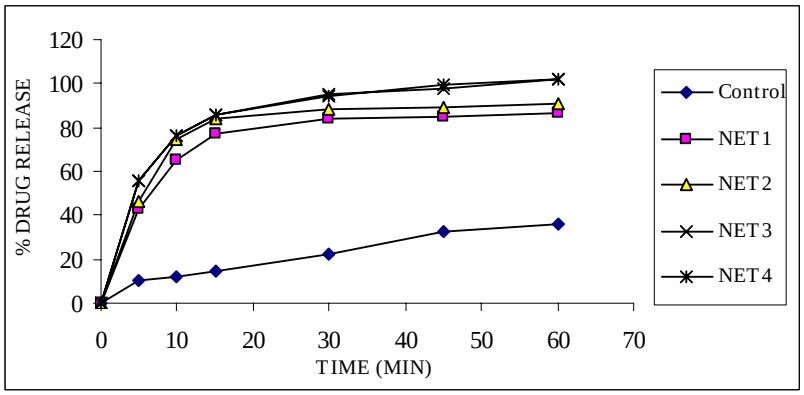


FIG NO: 6.28 COMPARATIVE DISSOLUTION PROFILE OF NEVIRAPINE 200mg IN 900 ml 0.1M pH 2 PHOSPHATE BUFFER 30th DAY STABILITY ANALYSIS

25ºC/60%RH



30ºC-65%RH



40ºC-75%RH

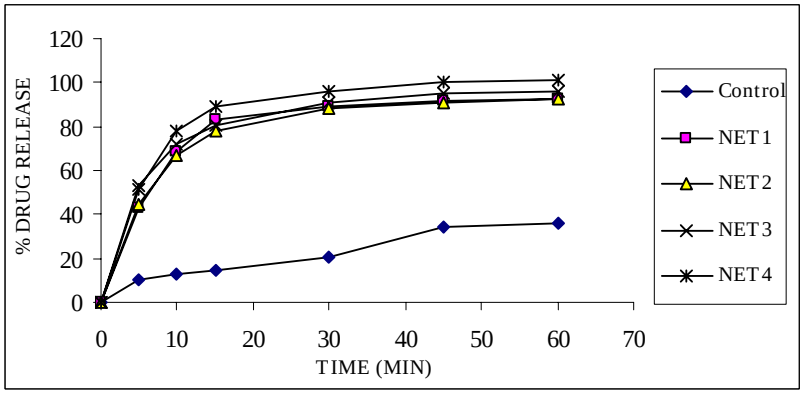
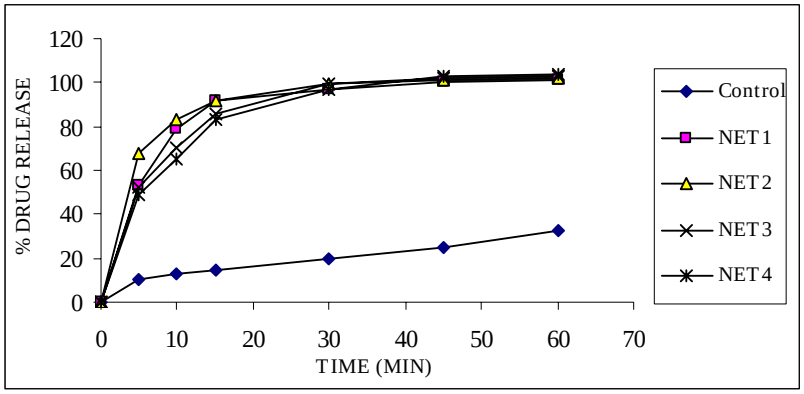
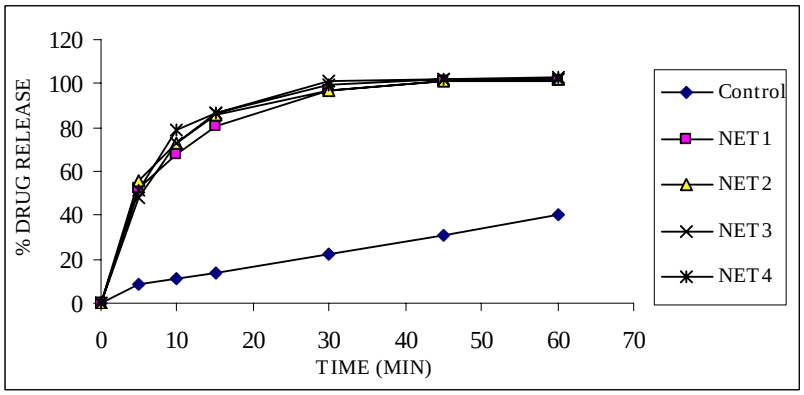


FIG NO: 6.29 COMPARATIVE DISSOLUTION PROFILE OF NEVIRAPINE 200mg IN 900 ml 0.1M pH 2 PHOSPHATE BUFFER 60th DAY STABILITY ANALYSIS

25ºC/60%RH



30ºC-65%RH



40ºC-75%RH

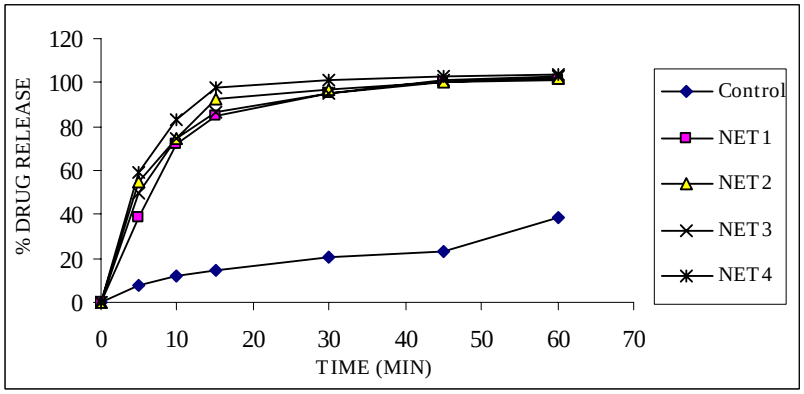


FIG NO: 6.30 COMPARATIVE DISSOLUTION PROFILE OF NEVIRAPINE 200mg IN 900 ml 0.1M pH 2 PHOSPHATE BUFFER 90th DAY STABILITY ANALYSIS

TABLE NO: 6.24 T_{50} AND T_{80} VALUES OF NEVIRAPINE (200mg) TABLETS AT 50 rpm WITH pH 2.0 PHOSPHATE BUFFER

TRIALS	T_{50} IN pH 2.0 PHOSPHATE BUFFER		T_{80} IN pH 2.0 PHOSPHATE BUFFER	
	900ml (COMPENDIA)	500ml (QUASI SINK)	900ml (COMPENDIA)	500ml (QUASI SINK)
NET_1	5.77	6.14	15.67	35.6
NET_2	4.49	5.20	14.17	27.92
NET_3	4.41	7.08	10.0	36.79
NET_4	3.47	7.08	7.66	16.53

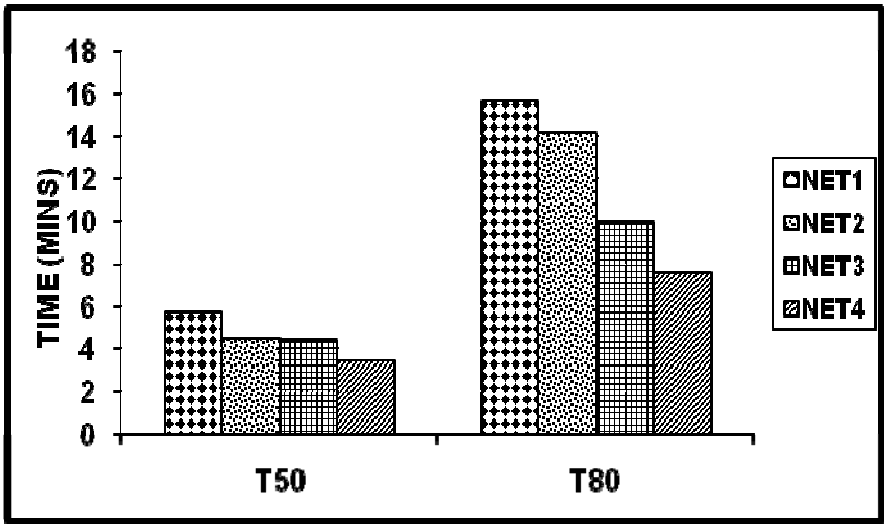


FIG NO: 6.11 T_{50} AND T_{80}VALUES OF NEVIRAPINE 200mg TABLETS AT 50 rpm IN 900 ml 0.1M pH 2 PHOSPHATE BUFFER (COMPENDIA MEDIUM)

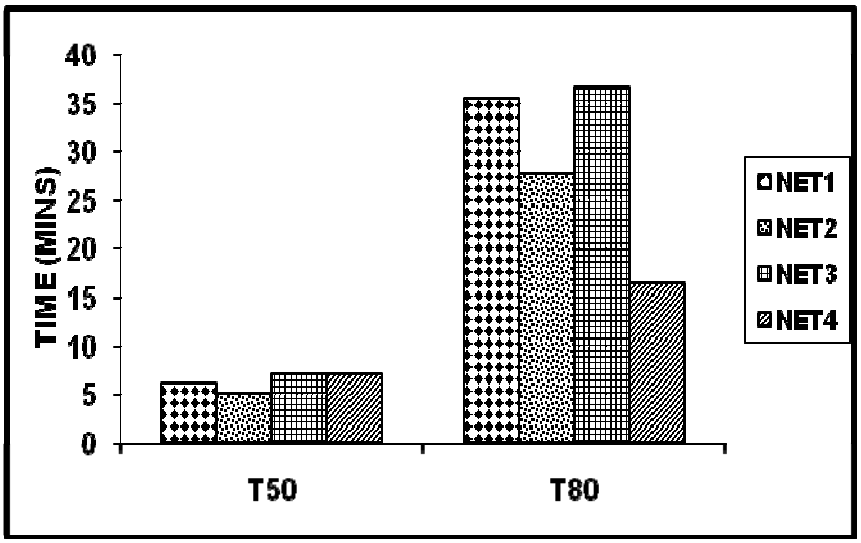
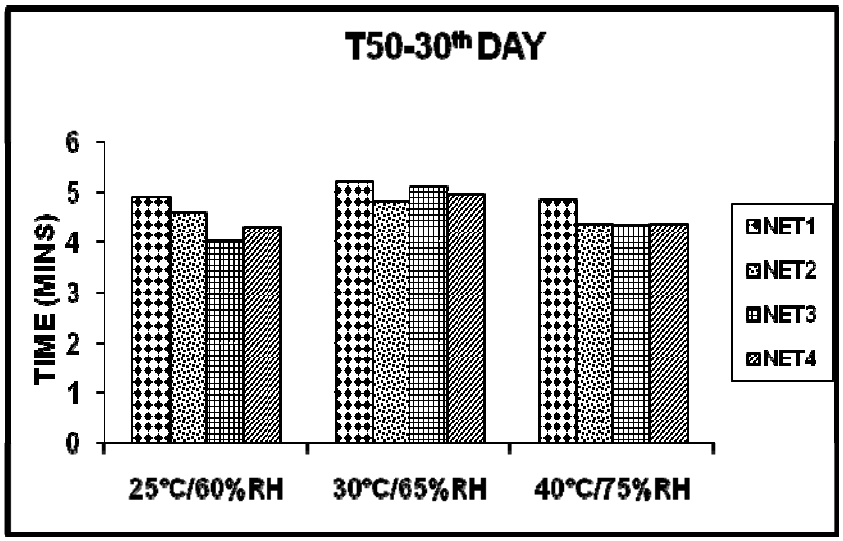


FIG NO: 6.12 T_{50} AND T_{80}VALUES OF NEVIRAPINE 200mg TABLETS AT 50 rpm IN 900 ml 0.1M pH 2 PHOSPHATE BUFFER (QUASI SINK MEDIUM)

TABLE NO: 6.27 T_{50} AND T_{80} DATA OF NEVIRAPINE 200mg TABLETS STABILITY ANALYSIS

TRIALS	DAYS	25ºC-60%RH		30ºC -65%RH		40ºC -75%RH	
		T_{50}	T_{80}	T_{50}	T_{80}	T_{50}	T_{80}
NET1	30	4.91	11.43	5.21	15.11	4.86	14.63
	60	5.05	13.05	6.09	20.05	5.92	14.24
	90	4.91	9.91	4.87	14.46	6.26	12.65
NET2	30	4.61	10.78	4.82	14.72	4.37	10.30
	60	4.48	12.99	5.41	12.21	5.80	16.99
	90	2.74	8.17	4.19	12.18	4.50	10.45
NET3	30	4.04	11.32	5.11	15.85	4.35	14.19
	60	5.08	18.28	4.12	11.71	4.53	14.28
	90	4.88	12.70	5.34	11.81	4.97	4.18
NET4	30	4.33	10.29	4.95	12.83	4.37	9.36
	60	4.98	12.48	4.09	11.82	4.88	10.66
	90	5.43	14.65	4.84	10.81	4.18	8.38



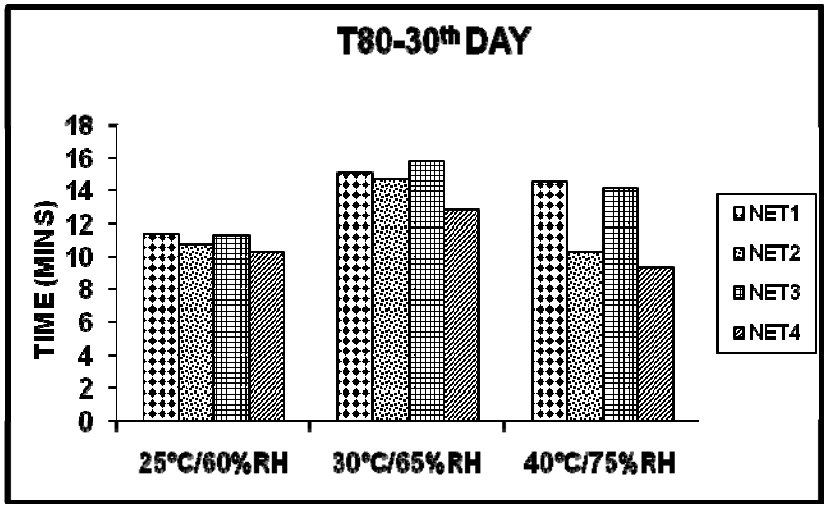
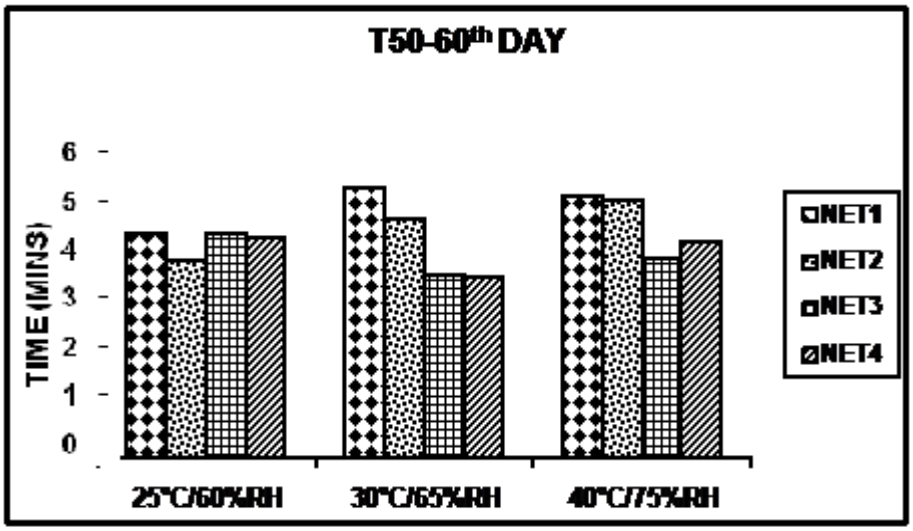


FIG NO: 6.31 COMPARATIVE T_{50} AND T_{80} DATA OF NEVIRAPINE 200mg TABLETS ON 30th DAY STABILITY ANALYSIS



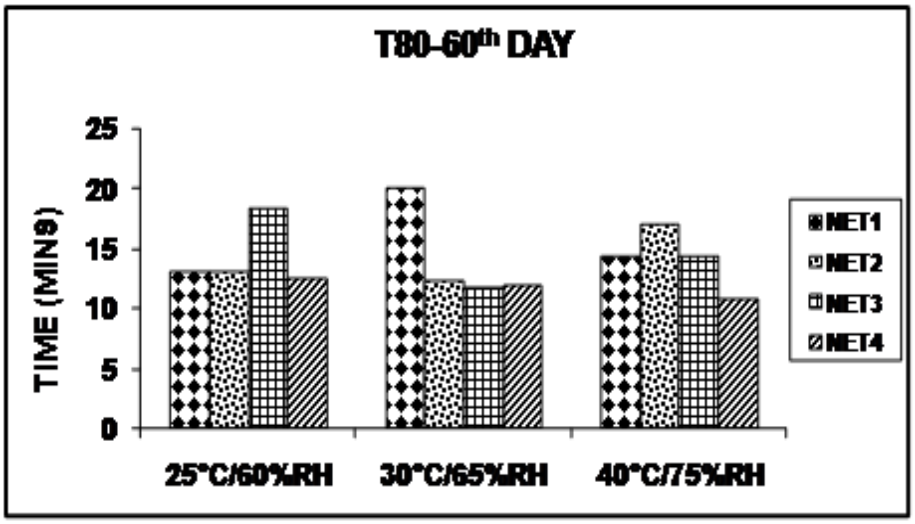
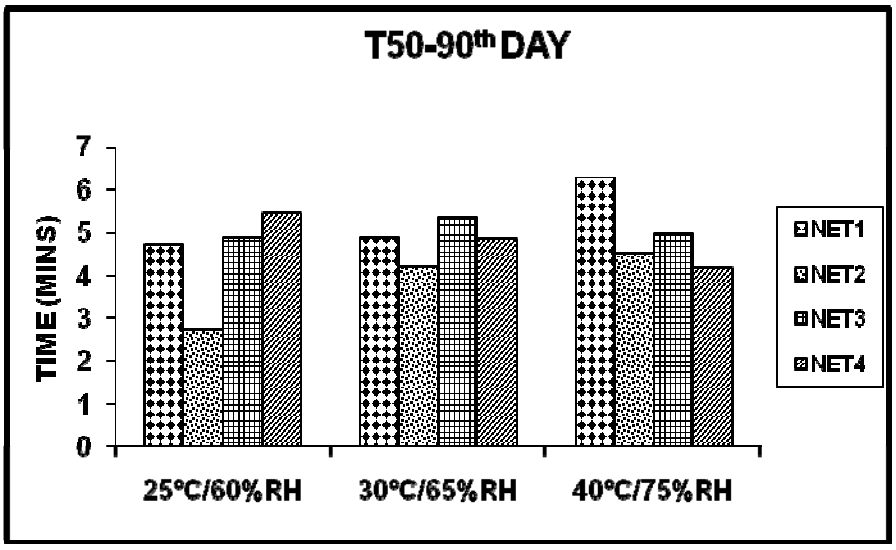


FIG NO: 6.32 COMPARATIVE T_{50} AND T_{80} DATA OF NEVIRAPINE 200mg TABLETS ON 60th DAY STABILITY ANALYSIS



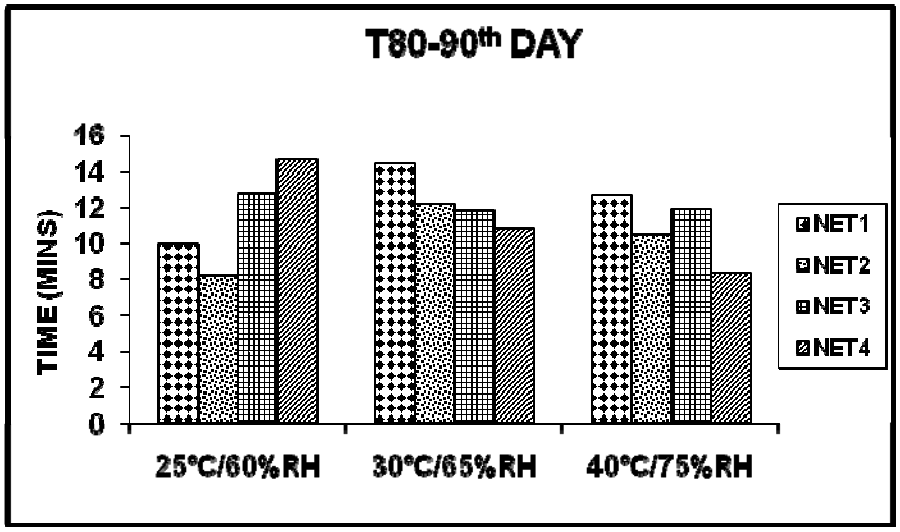
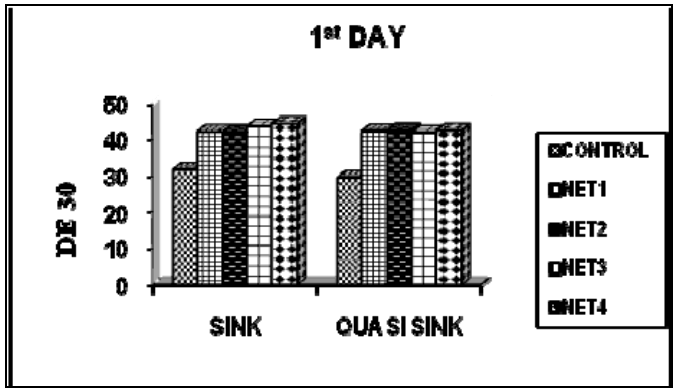
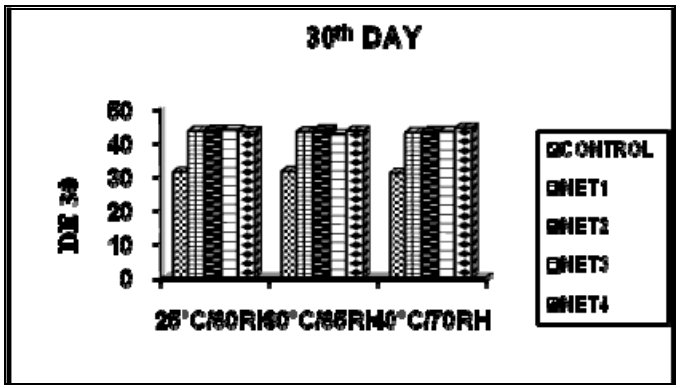
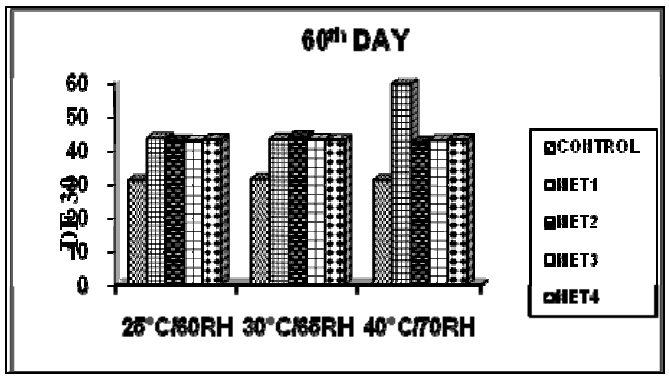


FIG NO: 6.33 COMPARATIVE T_{50} AND T_{80} DATA OF NEVIRAPINE 200mg TABLETS ON 90th DAY STABILITY ANALYSIS







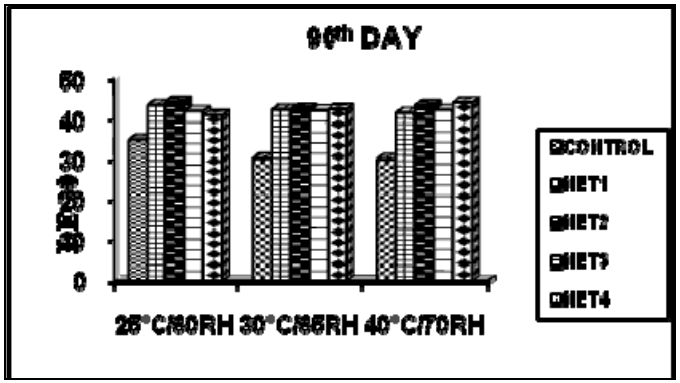


FIG NO: 6.15 Dissolution Efficiency (DE_{30}) of Nevirapine 200mg Tablets

7. CONCLUSION

All the drugs were selected for this study do not have adequate aqueous solubility and are in high dose drugs. In the disintegration test Polyplasdone XL10 crospovidone showed a better result than other superdisintegrants used in these studies.

In the in vitro drug release study, (Compendia medium and Quasi-sink medium) Polyplasdone XL10 crospovidone showed faster release when compared with other superdisintegrants used in this study.

From the result of $DE_{30,}$ Polyplasdone XL10 crospovidone having higher DE_{30} compared with other superdisintegrants used in this study.

In the stability study revealed that the developed formulations were stable in three different temperatures and humidity conditions for the period of three months according to ICH Guidelines.

This study demonstrated the effectiveness of Polyplasdone XL10 crospovidone as a superdisintegrant for these three poorly soluble drugs, and as Polyplasdone XL10 crospovidone recommended as a good disintegrant in tablet formulations of these poorly soluble drugs.

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